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ANNALS OF

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INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.

Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 13 (O.S., Vol. XVIII)

OCTOBER, 1939

NUMBER 4

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Subscription per volume or per annum, net postpaid, \$7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; \$7.50, other countries.

Entered as Second Class Matter at the Post Office at Lancaster, Pa. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph 4, section 538, P. L. & R., authorized October 7, 1936.

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ANNALS OF INTERNAL MEDICINE

VOLUME 13

OCTOBER, 1939

NUMBER 4

CULTURE OF HUMAN MARROW; STUDIES OF THE EFFECTS OF ROENTGEN-RAYS *

By EDWIN E. OSGOOD, M.D., and GEORGE J. BRACHER, M.D.,
Portland, Oregon

THE monographs on the biologic action of roentgen-rays by Duggar¹ and Scott² and on the effects of roentgen-rays on the blood and blood-forming organs by Selling and Osgood³ should be consulted for a review of the literature.

Most of the research on the action of roentgen-rays has been done on insect eggs, lower animals or plants and those studies which have been made on human material have necessarily not been quantitative nor adequately controlled. Much of this research has been done with doses far above any that are ever used in clinical therapy. Scott, therefore, very logically states:

(1) When any tissue is irradiated, careful measurement, both physical and biological, should be recorded. This may appear an obvious necessity, but neglect of the quantitative aspect of the biological action of radiations has been largely responsible for the errors, misunderstandings and controversies that are so apparent in the existing literature of the subject.

(2) More information about the processes by which cells recover from the effects of radiations, information which can be gathered by the experimental investigation of the time-factor, would be of immediate practical importance in radio-therapy.

(3) There is little knowledge about the physiology of the process of cell division. The study of the action of drugs on cell division and on the radio-sensitivity of cells seems likely to yield fundamental information, not only about the action of X and γ rays but also about the process of growth itself.

The development of the marrow culture method⁴ of growing human cells has made possible the application of controlled quantitative studies to living human cells.

* Read at the New Orleans meeting of the American College of Physicians, March 27, 1939 and at the Chicago meeting of the American Roentgen-Ray Society, Sept. 22, 1939.

From the Division of Experimental Medicine and the Department of Roentgenology, University of Oregon Medical School, Portland, Ore.

This work was made possible by a grant from J. Guy Strohm, M.D., Head of the Division of Urology, University of Oregon Medical School.

With the technical assistance of Evelyn A. Packham.

METHOD

A lead lined box (figure 1) was constructed with seven compartments just fitting the 30 c.c. vaccine vials containing the marrow. The box had two lead covers, one solid and one with an orifice the shape of a cross section of the 30 c.c. vials. These covers slide in a groove so that one vial may be exposed at a time while the others are protected. The effective-

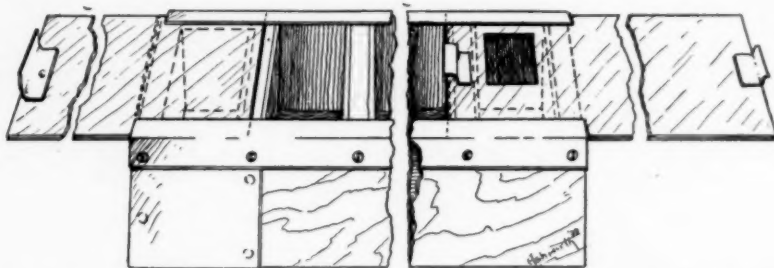


FIG. 1. Diagram of the box in which the vials containing marrow cultures were irradiated. There were 7 compartments, only 4 of which are shown. The sliding lead covers, of course, touched each other over a partition between 2 compartments while irradiation was given.

ness of this protection was tested by placing a dental film in the compartment with the control. The uniformity of the vials was tested by placing them side by side on a roentgen-ray film and taking a roentgenogram with low penetration. They gave shadows of uniform density which were less dense than those cast by the bones of the hand. The standardization of the dosage was made by E. D. Trout of the General Electric X-Ray Corporation. The actual r dosage was determined for each voltage, distance and filter used by placing the thimble ionization chamber inside of one of the vials the bottom of which had been cut off. Tests were made with the vial surrounded on three sides by lead of the same thickness as that in the box, with a layer of aluminum between the lead and the vial, and with the ionization chamber outside of the vial. These three methods gave almost identical results with the wave lengths employed, indicating that there was no appreciable absorption by the glass or scattered radiation from the lead or glass which would reach the cells.

About 10 c.c. of marrow were obtained from each subject by the technic of sternal puncture⁵ and the culture was prepared in a 50 c.c. vaccine vial as previously described.⁴ As a rule, about 50 c.c. of culture containing 2,000 nucleated cells per cu.mm. were obtained from one subject. The cultures contained both the mature and immature cells of the granulocyte series and the known highly radio-sensitive lymphocytes. The culture was thoroughly mixed and initial total and differential nucleated cell counts were done from which the absolute numbers of each cell type present were computed. Equal volumes, usually about 8 c.c., of the thoroughly mixed culture were then transferred to 30 c.c. vaccine vials which were handled

identically with the exception of the irradiation or colchicine. The controls were placed in the lead box along with the vials to be irradiated so that they were always side by side as well as being in and out of the incubator for the same lengths of time. At intervals samples were removed, the total and differential cell counts were repeated, and the absolute numbers of each cell type present were computed. In the early experiments leukocyte counting technic and a differential count of 500 to 1000 cells were used. In the later experiments, to reduce the counting error, the spinal fluid technic of counting was used and enough cells were included in the differential count so that at least 20 of the least numerous cell type were counted. This sometimes involved a differential count of several thousands of cells. The absolute number of each type of cell in the irradiated vials and in those containing colchicine was then calculated in percentage of the number of the same cell type in the control vial at the same time. The percentage and the time after irradiation were then plotted on graph paper as shown in figures 2 to 5. This method of presenting the results makes it possible to see at a glance the effects of the variable introduced since any deviation from the 100 per cent line represents a deviation from the corresponding count in the control. Actually, the effects of several variables on each cell type could be studied on cultures from one marrow but for clarity of presentation one variable will be discussed at a time and in the figures only a few cell types are included.

THE EFFECTS OF THE SAME DOSE AND WAVE LENGTH OF IRRADIATION ON THE DIFFERENT CELL TYPES *

Figure 2 shows the effects on the different cell types. Note that the fall in lymphocyte count begins early and that the decrease in lymphocytes is more rapid than in other cell types. The decrease in lymphocytes apparently begins immediately and gives a straight line curve, starting at the time of irradiation and levelling off again rather abruptly after an interval of time varying with the dose employed. The greater sensitivity of the lymphocytes was noted in all the 42 experiments which would test the relative sensitivity of the different cell types. The progranulocytes (promyelocytes) were the next most sensitive cells studied, but in none of the marrows investigated were granuloblasts (myeloblasts) numerous enough so that a count of statistically significant numbers was feasible. In most of the experiments the drop in progranulocytes (promyelocytes) occurred very early, but not enough counts were obtained in the first 12 hours after irradiation to be certain whether the curve of the fall is a straight line from the 0 time or whether, as appears in the experiment illustrated in figure 2, the count remains constant for a few hours before the fall begins. It is certain, however, that the decrease begins within the first 24 hours and con-

* The criteria of cell identification and the nomenclature used are described and illustrated in OSGOOD, E. E., and ASHWORTH, CLARICE M.: *Atlas of Hematology*, 1937, pp. 255, J. W. Stacey, Inc., San Francisco.

tinues for two to six days. The granulocytes (myelocytes) do not begin to fall until after 48 hours and then decrease gradually over a period of several days. The metagranulocytes (metamyelocytes) begin to decrease

EFFECTS OF SAME DOSE OF X-RAYS ON DIFFERENT CELL TYPES

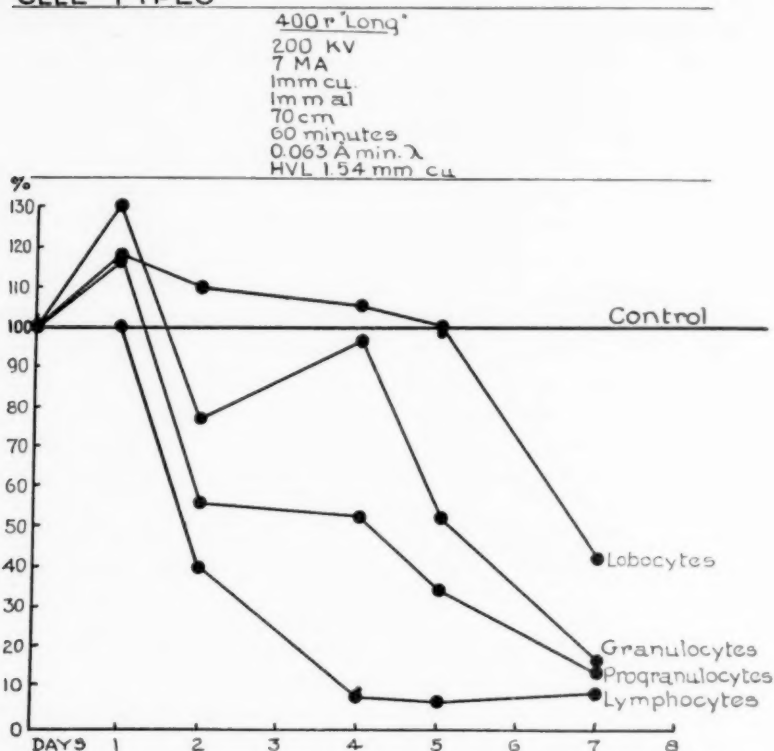


FIG. 2. In this and all subsequent figures, the curves represent actual results from a single experiment and are not averaged or smoothed. Any deviation from the 100 per cent line represents a deviation from the count for the corresponding cell type in the control examined at the same time. Smoothed curves for lymphocytes would probably show a straight line drop from 0 time similar to that shown in figure 3. Smoothed curves for progranulocytes (promyelocytes) would show a straight line drop beginning at or near 0 time but not as steep as for lymphocytes. The more mature cells of the granulocyte series in smoothed curves would show a straight line drop, leaving the 100 per cent line at progressively longer intervals after the beginning of irradiation the more mature the cell.

at about three days and the rhabdocytes (staff cells) begin to decrease at about four days, but these were omitted from the figure for the sake of clarity. The lobocytes (polymorphonuclears) begin to decrease at about five days. It is evident, therefore, that the lymphocytes are more sensitive than the other cells, and in the granulocyte series the effect is first observed on the more immature cells and later becomes manifest on the more mature cells. It is noteworthy that there was not a sudden initial drop and then a levelling off, nor was there any great increase over the control in the

numbers of disintegrating cells, as would have been the case if roentgen-rays directly killed the cells.

THE EFFECTS OF VARYING THE DOSE OF IRRADIATION

When all of the factors were kept constant and the total dose was varied by varying the time alone, results similar to those illustrated in the experiment shown in figure 3 were obtained. Fifteen marrow cultures were

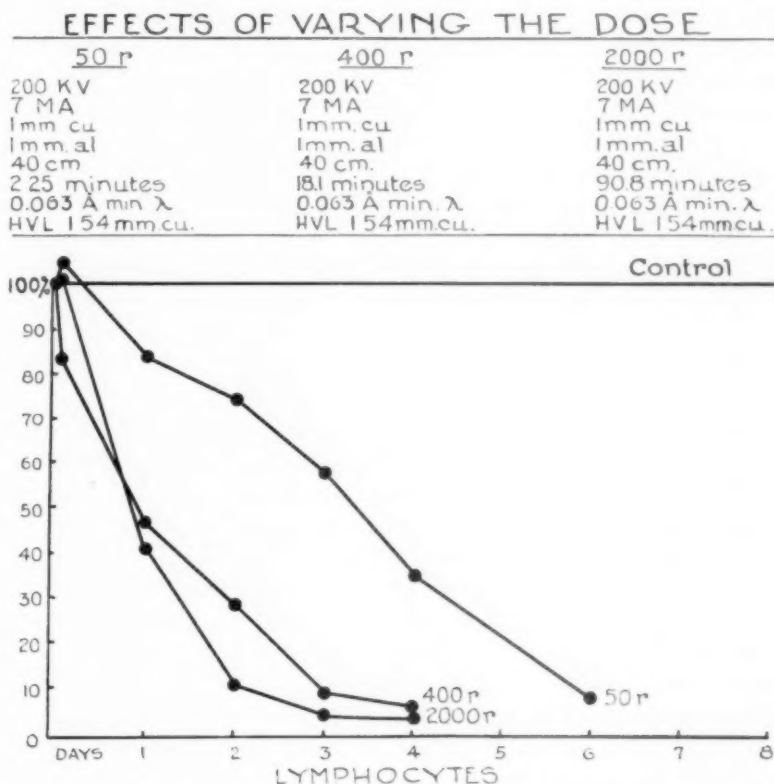


FIG. 3. Curves for the other types of cells had the same shape as illustrated and described in figure 2 and showed a similar difference with alteration in dose to that shown for lymphocytes. Note that there is a significant difference with variations in dose but that it is not directly proportional to the size of the dose.

studied on which the effects of two or more different doses of irradiation could be compared. The doses studied were 50, 75, 150, 300, 400, 500, 600, 1,000, and 2,000 r. Note that all of these doses are within the range of dosage used in treating human disease. In all the results were similar to those shown in the experiment illustrated in figure 3; namely, that within this range increasing the dose increased the effect by making the slope of the curve more steep but that the increase was not directly proportional to the dose. The quantitative effectiveness was not calculated as has been done

for insect eggs because of the great effect of the time after exposure on the number of cells remaining and the fact that most experiments did not continue longer than six or seven days when the cell counts were still decreasing. Experiments are under way to determine what levels are finally attained. It seems probable that the effects will vary with the square root of the dose as has been shown to be true for other cells. Enough work has been done to show that at least with the smaller doses there is a tendency for the cell counts eventually to become constant as shown in figure 3. The time at which this occurs varies for the different cell types and also for the different doses of irradiation. Doses as small as 50 r produce definite effects and doses of 2,000 r produce somewhat more effect than 1,000 r, so that it is evident that investigation of smaller and larger doses is needed before the minimal effective dose or the dose that produces a maximum effect on these cells can be stated.

Even when a dose of 2,000 r was used it did not result in the death of all the cells. Some of the lymphocytes survived a dose of 2,000 r although most disappeared after a dose of 50 r. Even with a dose of 2,000 r a significant fall in the numbers of lobocytes (polymorphonuclears) was not noted within the first four days. To find out whether the cells which, because of their normal morphology, were being counted as lobocytes (polymorphonuclears) and rhabdocytes (staff cells) were actually living, staphylococcus vaccine was added to the specimens removed from the cultures just before making the smears for differential counting and the percentage and absolute numbers of lobocytes (polymorphonuclears) and rhabdocytes (staff cells) containing phagocytosed cocci were compared with the corresponding values in the control. In both control and irradiated cultures, over 85 per cent of the lobocytes (polymorphonuclears) contained organisms. This was true even when the marrow had received a dose of 2,000 r until the fourth day when the lobocyte (polymorphonuclear) count had begun to fall. The slope of the curve for the cells containing phagocytosed organisms in percentage of the corresponding control cells was the same within the experimental error of the method. It seems justifiable to conclude from this that even a dose of 2,000 r does not kill lobocytes (polymorphonuclears). One of us has shown⁶ that the length of life of the lobocytes (polymorphonuclears) averages only 60 hours and varies from 48 to 90 hours so that the lobocytes (polymorphonuclears) present at the time of irradiation would all have lived out their life span before a drop in lobocytes (polymorphonuclears) began.

THE EFFECT OF VARYING THE WAVE LENGTH

Varying the wave length within the limits used (figure 4), keeping the dose in r units constant, did not produce any significant differences in results. However, only five experiments were done and the hardest and softest rays used were those shown in the figure. The whole range of wave lengths,

up to gamma rays of radium and down to grenz rays, remains to be investigated.

THE EFFECT OF VARYING THE TIME

The effects of varying the time, keeping the total dose constant by varying the distance of the tube, are illustrated by the experiment shown in

EFFECTS OF VARIATION IN WAVE LENGTH

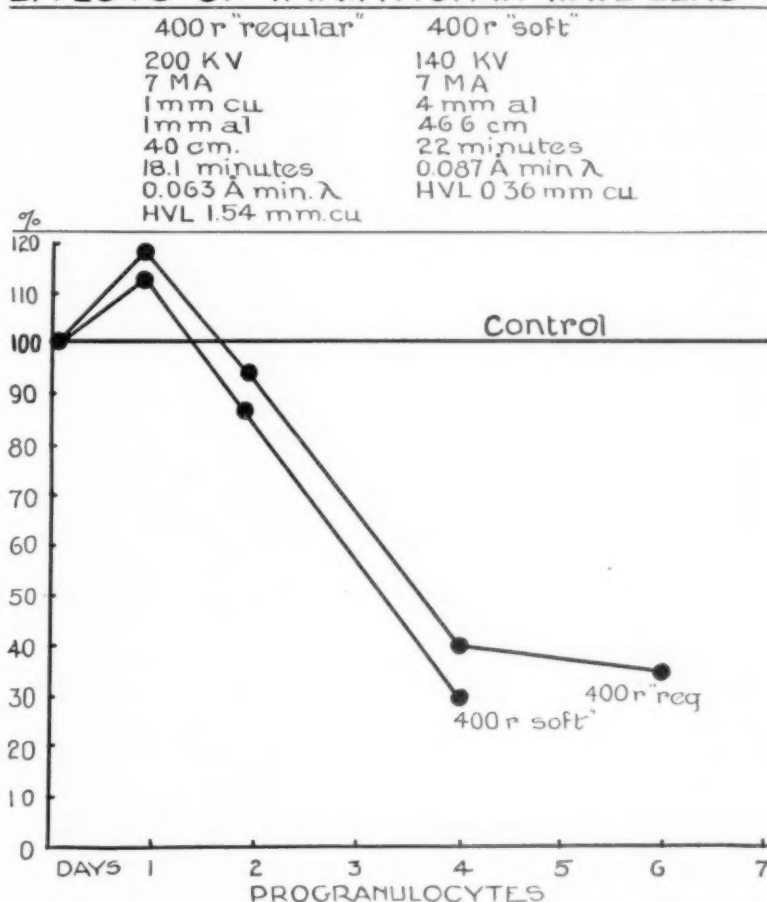


FIG. 4. Note that the same dose given at widely different wave lengths shows no significant difference in effect. This applied to the other cells studied as well as to the progranulocytes (promyelocytes).

figure 5. Within the time range of 5 to 60 minutes which was the greatest difference employed, no significant differences in effect were noted with either 400 r or 50 r. However, further work with greater differences in time of exposure, varying from the time used in radium therapy down to the minimum time in which an equivalent dose of roentgen-rays may be given with the most powerful equipment, should be investigated.

THE EFFECT OF FRACTIONAL EXPOSURES

Only one experiment on this has been completed and in this only two exposures were made about six hours apart, using doses of 200 r and 200 r with the factors shown in figure 5. No significant differences were noted

EFFECTS OF VARYING THE DISTANCE

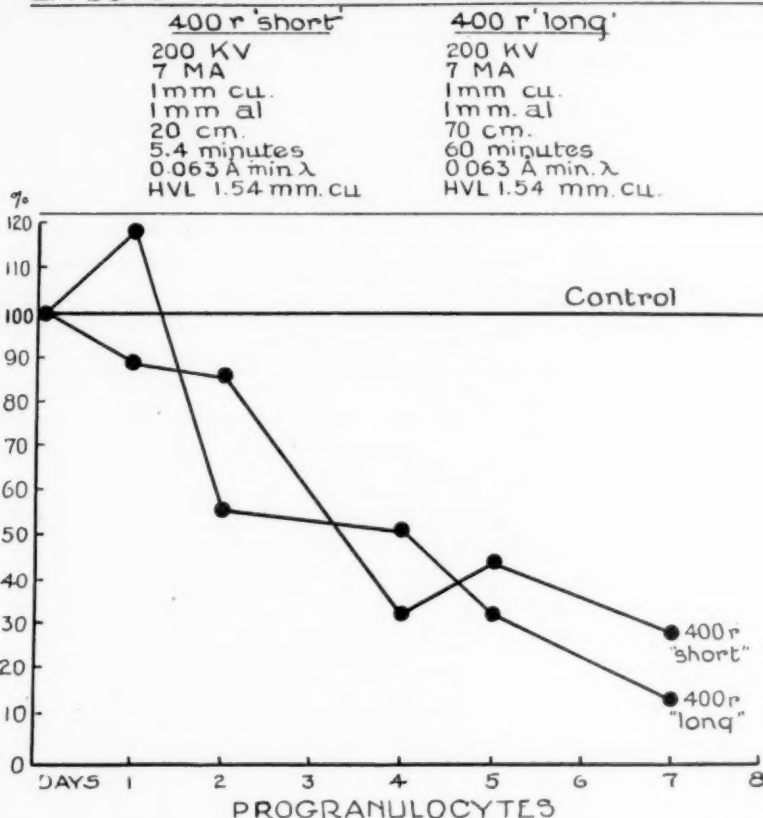


FIG. 5. Note that varying the time by varying the distance of the tube, keeping all other factors constant, did not significantly alter the effect. This was true for other doses and for the other cell types as well as for progranulocytes (promyelocytes).

in this experiment between the cells exposed to a dose of 400 r at the time of the first fractional dose and the divided exposures but much more work should be done before conclusions are justified.

THE EFFECT OF TRANSFERRING CULTURE MEDIUM FROM IRRADIATED VIALS TO NONIRRADIATED VIALS AND VICE VERSA

It is well known that in leukemias and sometimes Hodgkin's disease and lymphosarcoma, irradiation of one area may be followed by diminution in size of lymph nodes that were not irradiated. Some have thought that this might be explained by the production of some substance circulating in the

blood through which the action of roentgen-rays was mediated. To investigate this possibility, 2 controls were placed in the box side by side with two vials which were given identical doses of roentgen-rays. Immediately after irradiation in some studies and 20 hours after irradiation in others the vials were centrifugated and the supernatant fluid from one of the controls and one of the irradiated cultures was withdrawn and the fluid from the control placed in the vial containing irradiated cells and the fluid from the irradiated cultures placed in the vial containing nonirradiated cells. In the experiments in which this was done the irradiated cells with nonirradiated medium showed a curve of decrease similar to that for the culture with irradiated cells and medium; whereas, the nonirradiated cells with medium which had been irradiated showed no significant deviation from the control. These experiments would suggest that in the time after irradiation studied no humoral mechanism was involved in the action of irradiation but that this action was directly on the cells. Many more experiments with transfer of medium at different time intervals are obviously needed before a humoral action can be excluded.

THE EFFECTS ON MITOTIC AND AMITOTIC CELL DIVISION

Previous studies⁷ with the marrow culture method have shown that progranulocytes (promyelocytes), prolymphocytes, promonocytes and all of the blast cells undergo mitotic division; that the lymphocytes, plasmacytes and prokaryocytes (erythroblasts) undergo only amitotic division; and that the cells of the granulocyte series more mature than the progranulocyte (promyelocyte) do not divide. In the marrow cultures which have been used in these experiments, lymphocytes and progranulocytes (promyelocytes) are the only cells that divide which have been present in sufficient numbers to make counts practical. It was early observed that mitoses which were readily found in the control cultures were not seen in the irradiated cultures, but since less than 1 per cent of the cells in the controls were ordinarily in mitosis it was difficult to count enough cells to get statistically significant figures for the cells in mitosis. Since colchicine has been shown⁸ to stop mitosis in the metaphase it was used as an indicator of the effects on mitosis. Preliminary experiments indicated that some mitoses were affected* by concentrations of colchicine as low as 1-10,000,000 but that all mitoses were not affected by concentrations much less than 1-100,000. In those marrows which were studied with concentrations of 1-100,000 no mitoses were found not showing typical colchicine effects. It is not definitely known whether colchicine has other effects on the cells than stopping mitosis nor is it known for certain whether colchicine merely slows cell division resulting in ultimate reformation of a nucleus and maturation, or whether the cell eventually dies. It was observed, however, that the number of progranulocytes (promyelocytes) showing colchicine mitoses progres-

* See figure 1 in OSGOOD, E. E.: Culture of human marrow as an aid in evaluation of therapeutic agents: studies of sulfanilamide and related compounds, *Jr. Lab. and Clin. Med.*, 1939, xxiv, 954.

sively increased for a period of time and then decreased, indicating that the cells must either disintegrate or that the nucleus must eventually reform and the cells mature.

In studying the effect of roentgen-rays on mitosis a control culture without colchicine or irradiation was studied, also a culture with 1-100,000 colchicine alone, a culture with 1-100,000 colchicine irradiated with a dose of 400 r, and a culture with 400 r irradiation alone. Experiments were done in which the colchicine was added 20 hours before irradiation and others in which the colchicine was added immediately after irradiation. In one of the experiments in which colchicine was added 20 hours before irradiation, the culture containing colchicine alone, studied 40 hours after addition of the colchicine, showed mitosis stopped in the metaphase in 57 of the 100 progranulocytes (promyelocytes) counted. At the same time in the culture containing colchicine, which was irradiated 20 hours before, no mitoses were found in counting 100 progranulocytes (promyelocytes) and only three were found in a half hour's search using an 8 mm. objective and a magnification of $200\times$ which permitted a survey of thousands of cells. By 68 hours after irradiation, two colchicine mitoses in about 3,000 cells could be found in the irradiated culture containing colchicine and mitoses were still numerous in the culture containing colchicine alone. Mitoses were still very scarce at four and five days in the irradiated culture which contained colchicine. This experiment would seem to show that roentgen-rays prevented the onset of mitosis since any mitoses occurring during this time should have been stopped by colchicine.

Lymphocytes in amitotic division were found in control cultures and seemed less numerous in irradiated cultures. However, no method of arresting amitotic division was available so statistically significant counts were not obtained. The decrease in lymphocytes gave such smooth, straight line curves without increase in disintegrating lymphocytes that a decreased production rather than increased destruction seems most probable.

COMPARISON OF THE EFFECTS OF ROENTGEN-RAYS AND COLCHICINE

Quantitative studies of each cell type were made in the studies on mitosis using colchicine as an indicator. Since colchicine held mitosis in the metaphase and some investigators have thought that the major effect of roentgen-rays occurs during mitosis, it seemed possible that the roentgen-rays and colchicine might have an additive effect. The results observed, however, were that colchicine had no effect on the lymphocytes, as would be expected, since lymphocytes have never been observed in mitotic division, and that the effect of colchicine alone on the cells of the granulocyte series was to give curves similar in character and slope to those obtained with roentgen-rays. Most interesting of all, the combination of roentgen-rays and colchicine showed no additive effect on the cells of the granulocyte series, the curves agreeing within the limits of experimental error with the curves for the culture containing colchicine alone and also for the culture receiving 400 r

of roentgen-rays alone. On the other hand, the lymphocytes in the culture receiving both roentgen-rays and colchicine showed a curve corresponding to the culture receiving roentgen-rays alone and not to that containing colchicine alone. Unfortunately, only a few experiments were completed using colchicine as indicator and the concentration of 1-100,000 is above the concentration which is fatal to human beings and animals. More work is in progress on the comparative effects of colchicine, roentgen-rays and combinations of the two since this line of investigation seems to offer great promise.

THE EFFECT OF IRRADIATION ON THE MORPHOLOGY OF THE CELLS

The majority of the cells in the irradiated cultures were similar in morphology, motility, and phagocytic ability to the corresponding cells in the control nonirradiated cultures. However, a few cells with giant bizarre shaped nuclei were noted in the cultures receiving irradiation. These changes in the nucleus were first noticed in the progranulocytes (promyelocytes) and from day to day the cells showing alterations would be more mature, next appearing as granulocytes (myelocytes), then metagranulocytes (metamyelocytes), rhabdocytes (staff cells), and finally as lobocytes (polymorphonuclears). The structure of the nucleus was similar to that described by O. P. Jones⁹ for the cells of the granulocyte series in the sternal marrow of patients with pernicious anemia. A few such cells were found in the control cultures, also, and they are occasionally found in other cultures. It seems possible that these cells may represent polymers or other chromosomal aberrations and that roentgen-rays increase the number of mutant cells over those which naturally occur. Our data, however, are not sufficient to prove this.

COMPARISON OF THE EFFECTS OF IRRADIATION ON LEUKEMIC AND NONLEUKEMIC CELLS

Studies of the effects of irradiation on marrow or blood cultures from four cases of chronic granulocytic (myelogenous) leukemia and three cases of lymphocytic leukemia have been compared with cultures of nonleukemic cells. The curve for each type of cell fell within the limits of variation noted for the same irradiation on the corresponding nonleukemic cell, except in one patient with chronic granulocytic (myelogenous) leukemia who had received a total of 700 r of irradiation to the chest and 300 r to the spleen, given every two days in doses of 100 r, the last treatment being two days before marrow was obtained for culture. In this patient there was distinctly less effect than for a similar dose of roentgen-rays on nonleukemic cells of the same type. Since in this type of experiment different marrow cultures have to be compared, the control is not as adequate as in the other experiments and a much larger series must be studied before it can be concluded that there is no difference in the type of effect on leukemic and nonleukemic cells.

COMMENT

Any theory of the action of roentgen-rays on these marrow cultures must explain the gradual decrease in cell count without a corresponding increase in disintegrating cells. It must explain the latent period before the effects become manifest on the more mature cells of the granulocyte series. It must explain the fact that the lobocytes (polymorphonuclears) are not killed in a period of four days by even such large doses as 2,000 r, and the fact that a few of the most sensitive cells, such as the lymphocytes and progranulocytes (promyelocytes) may still be found several days after large doses have been given although most of the cells have disappeared before this. It must explain the absence of mitotic figures even when colchicine is used as an indicator and the fact that the effects of colchicine on cells of the granulocyte series are similar to the effect of roentgen-rays but are not similar on lymphocytes which undergo only amitotic division.

It can be shown mathematically that if the action of roentgen-rays were to prevent the occurrence of either mitotic or amitotic division in the cells and if only the progranulocytes (promyelocytes) among cells of the granulocyte series were capable of division that curves of this general shape would result and there would be no increase in the rate of cell death but only a decrease in the rate of cell multiplication. The effects might be compared to those which would occur in a population group of human beings if reproduction occurred only in newborn infants and all or many of the newborn infants were sterilized. A decrease in the number of newborn would first be noted as they matured to childhood; then the number of children would decrease as they matured to adolescence, and so on. The natural death rate of a particular group would not be altered, so that deaths would not increase in number in proportion to the number of the population alive at any age period, and the total number of deaths in a given time period would not increase although the population would eventually decrease.

The theory that roentgen-rays act only on cells in the process of division seems improbable since the number of cells affected is far greater than the number of cells found in the process of division at any one time. It is possible, however, that there is a certain time period in the intervals between division when cells are more sensitive than at other time periods. If this were the case, the same dose of roentgen-rays given over a period of the entire cycle from one division to the next for the cell type would be expected to have a greater effect than the same dose given in a short period of time. Judging from the number of cells in mitosis and the probable duration of mitosis in human cells, the duration of the cycle between cell division in these cells is probably of the order of 24 to 100 hours and if this were the case, differences would hardly be expected from variations in the time of exposure of only 5 minutes to 1 hour, but a difference with times of exposures such as are usually used in radium therapy would be expected. Work is in progress to investigate this possibility.

These experiments do not exclude a hastening of maturation as suggested by Isaacs.¹⁰ However, the increased proportion of more mature cells could be explained by a simple decrease in cell division among the immature cells with resultant aging of the cell population.

SUMMARY

The marrow culture method makes possible quantitative studies of the effects of irradiation on living human cells of different radio-sensitivity and stages of maturity. This preliminary study of several of the possible variables in roentgen-ray therapy indicates that this method should give information of value and suggests that irradiation in the doses employed in clinical roentgen therapy does not directly kill cells but does inhibit multiplication resulting in a gradual decrease in the cell populations as they mature and die. Colchicine should prove a valuable indicator of the effects of irradiation on mitotic division. Irradiation apparently inhibits amitotic division as well as mitotic division. Much work remains to be done with the method before final conclusions are warranted.

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SULFANILAMIDE AND MENINGITIS *

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THE therapy of infections has developed almost exclusively along the lines of specificity, and an excellent example of this is the use of the many types of anti-serum for the treatment of pneumococcus pneumonia. Likewise in drug therapy, the real successes have been mostly specific in their application. Used at first as a specific in beta hemolytic streptococcus infections, the therapeutic trial of sulfanilamide and its derivatives has been extended clinically and experimentally to cover the most remarkable variety of infections. This list includes such dissimilar organisms as gram positive and negative micrococci, aerobic and anaerobic bacilli, acid fast bacilli, spirochetes, protozoa and even filterable viruses. Such reputed panaceal properties are beyond the realm of specificity, and experimental investigations do not speak for bacterial specificity but rather indicate a bacteriostatic^{1, 2} or indirect bactericidal³ effect against microorganisms widely diverse biologically. This mode of action suggests a new approach in therapy. The actual practical value of this bacteriostatic or bactericidal effect has yet to be defined in clinical terms. Meanwhile careful experimental and clinical studies will probably tend to reduce the exaggerated expectations as to the therapeutic possibilities of the drug as well as establish its proper status.

In experimental work, the survival or death of the animal is the criterion of the success or failure of the therapeutic experiment. It occurred to us that analogous conditions are available clinically in a disease like meningitis. Meningitis, produced by the streptococcus, pneumococcus, staphylococcus, influenza bacillus and tubercle bacillus as well as some rare organisms, is almost invariably fatal, regardless of the treatment. Tripoli's⁴ mortality rate for 247 cases of meningitis due to other organisms than the meningococcus was 98.3 per cent. Meningitis, due to any of these organisms, should therefore offer an excellent testing ground for the therapeutic worth of sulfanilamide, as recovery in such a disease may almost unquestionably be ascribed to the drug. Meningococcus meningitis also, with or without specific serum treatment, has such a mortality that a substantial reduction in the death rate under sulfanilamide therapy should be significant.

The following 22 cases of meningitis are offered as illustrations of the

* Received for publication June 25, 1938.

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We wish to thank the Staffs of Hahnemann, St. Luke's and West Jersey Hospital for permitting us to treat these cases.

The sulfanilamide used was kindly furnished by the Abbott Laboratories and the Winthrop Chemical Co.

therapeutic value and action of sulfanilamide. They are discussed, along with sulfanilamide treated meningitis cases found in the literature, under the various types of infection. Our cases were treated practically exclusively with sulfanilamide, given either orally, subcutaneously or intrathecally.

Hemolytic Streptococcus Meningitis. It is safe to say that in the past a patient with streptococcic meningitis was regarded as an almost certain fatality. It is true occasional cases recovered, but these were so rare that the literature of recovery is one of single case reports, in which the outcome is ascribed to most varied methods of treatment. Gray,⁵ in his comprehensive review, estimated the mortality at over 97 per cent. Long and Bliss⁶ say the fatality rate in hemolytic streptococcus meningitis is about 99 per cent. Canfield's⁷ mortality was 97 per cent, Zeligs's⁸ 98 per cent and Tripoli's⁴ 91.6 per cent. In the 37 available cases at Johns Hopkins Hospital⁹ in the last 15 years, there was not a single recovery. Neal and Applebaum¹⁰ state that among 274 cases of various types of streptococcus meningitis, there was a death rate of 94.5 per cent.

Under sulfanilamide, there tends to be almost a reversal of these figures and, as Neal and Applebaum¹⁰ remark, the results seem quite astounding. Whether the credit is due entirely to sulfanilamide or whether the present strains of streptococcus are less virulent or whether these results will continue remains to be seen. Of 28 cases of hemolytic streptococcus meningitis of which Long and Bliss⁶ have knowledge, 85 per cent recovered under the drug. Applebaum¹¹ reports 26 cases of otitic or sinus origin with a recovery rate of 80.7 per cent. Trachsler¹² had four recoveries out of seven, but one of the fatal cases was due to a *Streptococcus viridans*. Carey¹³ had four cases of hemolytic streptococcus meningitis treated with sulfanilamide, all of which recovered. Arnold had six cases, all recoveries, but these are probably included in Long and Bliss's⁶ list. Some of the foregoing cases received also antimeningococcus or antistreptococcus serum or some adjuvant treatment such as transfusions, but these methods produced almost no recoveries before and it is questionable whether they act synergistically with sulfanilamide. Single case reports have the disadvantage of recording, as a rule, only successes. It is important to report failures with this treatment as well as successes to get an accurate estimate of its value.

Our own six cases of hemolytic streptococcus meningitis (table 1) received sulfanilamide only and no serum, although some were transfused when convalescent. Our figures for recovery are lower than others, four out of six or 67 per cent. The results are still in striking contrast with the presulfanilamide era. Of the 70 cases cited here, including our own, 57 or 81.4 per cent recovered.

Streptococcus viridans Meningitis. Meningitis due to *Streptococcus viridans* is much less common than that due to the beta hemolytic strep-

TABLE I
Streptococcus Hemolyticus Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— S. M. 16 yrs. male	6- 5-37 2nd day of disease	Nuchal rigidity. Lethargic	102°	Opalescent 330 cells mostly polys	Hemolytic streptococcus	0.8% Sulfanilamide 30 c.c. intrathecally 170 c.c. subcutaneously 30 c.c. intrathecally 170 c.c. subcutaneously
	6- 6-37	Same	102.2°	Same	Sterile	Same
	6- 7-37	Generally better	99.6°	Same	Sterile	30 c.c. intrathecally 100 c.c. subcutaneously
	6- 8-37	Improved	99.0°	Same		20 c.c. intrathecally 150 c.c. subcutaneously
	6- 9-37		98.6°	450 cells	Sterile	Sulfanilamide 15 grains every 6 hours
Recovered	6-27-37	Discharged				No medication since 6-12-37
No. 2— H. K. 7 yrs. male	6-30-37 3rd day of disease	Headache, photophobia. Positive Kernig	105.8°	Cloudy, 6,800 cells	Hemolytic streptococcus	0.8% Sulfanilamide 10 c.c. intrathecally 115 c.c. subcutaneously
	7- 1-37	Mastoidectomy, 6-30	103.8°	Cloudy	Sterile	10 c.c. intrathecally 115 c.c. subcutaneously 10 c.c. intrathecally 115 c.c. subcutaneously
	7- 2-37		102.0°	Cloudy		Same
	7- 3-37	Slightly better	101.0°	Cloudy	Sterile	10 c.c. intrathecally 115 c.c. subcutaneously
	7- 4-37		101.4°			Same
	7- 5-37	Improved	100.0°	Opalescent		Same, plus blood trans- fusion, 200 c.c.
	7- 6-37	Improved	98.8°			125 c.c. subcutaneously
Recovered	7-26-37	Discharged. Wound still healing	98.8°			30 grains daily from 7-7 to 7-15. No further med- ication
No. 3— J. S. W.	12-21-37 2nd day of disease	Stuporous. Nuchal rigidity	104.6°	Purulent	Hemolytic streptococcus	0.8% Sulfanilamide 15 c.c. intrathecally 110 c.c. subcutaneously 30 grains orally
	12-22-37		105.6°			60 grains orally
Died	12-23-37	Died 29 hrs. after admission and 48 hrs. after onset of meningitic symptoms. Autopsy—Right mastoiditis. Purulent meningitis				

TABLE I (Continued)

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 4— E. S. 6 yrs. female	2-20-38 2nd day of disease	Semi-conscious	105.4°			
	2-21-38	Nuchal rigidity	105.0°			
	2-22-38	Positive Kernig. Otitis media	103.0°	Slightly cloudy 608 cells	Hemolytic streptococcus	60 grains sulfanilamide
	2-24-38		103.0°	1500 cells	Hemolytic streptococcus	30 grains sulfanilamide
	2-29-38	Slight improvement	103.8°	300 cells		30 grains daily since 2-24-38
	3- 4-38		101.0°	Purulent. 1 c.c. obtained	Hemolytic streptococcus	Same
	3-12-38	Condition same	100.0°	Same	Same	0.8% Sulfanilamide 8 c.c. intrathecally 115 c.c. subcutaneously
	3-13-38		100.0°			8 c.c. intrathecally 115 c.c. subcutaneously
	3-16-38	Comatose hemiplegia	102.4°			Blood transfusion 150 c.c.
	3-21-38	Died	107.0°			
No. 5— J. L. 8 yrs. male	3-10-38 4th day of disease	Delirious. Nuchal rigidity. Photophobia. Mastoidectomy	102°	682 cells	Hemolytic streptococcus	0.8% Sulfanilamide 10 c.c. intrathecally 30 grains orally
	3-11-38		105°	700 cells	Sterile	10 c.c. intrathecally 260 c.c. subcutaneously 25 grains orally
	3-12-38	Improved	103°	540 cells		6 c.c. intrathecally 125 c.c. subcutaneously Blood transfusion 250 c.c.
	3-13-38		102°			10 c.c. intrathecally 120 c.c. subcutaneously 15 grains orally
	3-15-38	Feels better		680 cells	Hemolytic streptococcus	9 c.c. intrathecally 25 grains daily, orally
	3-18-38	Greatly improved	99°	380 cells	Sterile	20 grains orally daily
	3-22-38		98.6°			15 grains daily since 3-19-38
	4- 6-38	Mastoid wound healing. Discharged				

TABLE I (Continued)

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 6— A. A. 12 yrs. female	5- 2-38	Delirious. Photophobia. Marked nuchal rigidity, positive Kernig	103.4°	7500 cells	Hemolytic streptococcus	0.8% Sulfanilamide 12 c.c. intrathecally 113 c.c. subcutaneously 18 c.c. intrathecally 107 c.c. subcutaneously 15 grains orally
	5- 3-38	More rational	102.6°	5000 cells	Sterile	10 c.c. intrathecally 8 c.c. intrathecally 115 c.c. subcutaneously 30 grains orally
	5- 4-38	Clinically improved. Rigidity. Positive Kernig still present	101.0°	6400 cells	Sterile	10 c.c. intrathecally 35 c.c. subcutaneously 30 grains orally
	5- 5-38	Generally better	100.6°	1400 cells	Sterile	10 c.c. intrathecally 105 c.c. subcutaneously 30 grains Blood transfusion 250 c.c.
	5- 6-38	Continues to improve	100.2°			40 grains orally
	5- 7-38	Better	100.0°			40 grains orally
	5- 8-38	Generally better	100.8°			40 grains orally
	5- 9-38	Rigidity slight but generally better	99.0°			30 grains orally
	5-10-38	No complaint	99.0°			30 grains orally
	5-11-38	No complaint	98.6°			20 grains orally
	5-12-38	No complaint, apparently recovered. Kept for further observation	98.6°			
Recovered						

tococcus. In Neal, Jackson and Applebaum's¹⁴ series of 205 cases of streptococcus meningitis, the hemolytic types were about 10 times as numerous as the non-hemolytic forms. Applebaum¹¹ has three cases of non-hemolytic streptococcus meningitis of otitic origin treated by sulfanilamide. One case recovered. Trachsler's¹² one case died in spite of sulfanilamide but there was a possible complication of basal fracture. We treated two cases (table 2). One case was in a desperate condition when seen and, although treated intensively with sulfanilamide, survived only 15 hours after admission to the hospital. The other case responded to the drug treatment satisfactorily, but the organism isolated was difficult to place. Morphologically, it resembled a pneumococcus more than a streptococcus but failed to type with any of the 32 antisera. This result was confirmed at two other laboratories. The organism was not bile soluble, produced a green zone on human, rabbit and horse blood agar plates and we finally concluded it was a *Streptococcus viridans*. This gives two recoveries out of six cases, a mortality of 67 per cent.

Mellon and Cooper,¹⁵ in discussing the biphasic nature of certain Group A hemolytic streptococci, speak of the possibility of sulfanilamide being misinterpreted as curing *Streptococcus viridans* infections which are really caused by hemolytic streptococci stabilized in a viridans phase. This might apply to some of the cases reported.

TABLE II
Streptococcus viridans Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— R. P. 5 yrs. male	10-22-37 2nd day of disease	Moderate nuchal rigidity. Positive Kernig. Nasopharyngitis	102.6°	576 cells	<i>Streptococcus viridans</i>	55 grains sulfanilamide orally
	10-23-37	Photophobia	102.4°	Slightly cloudy	Same	0.8% Sulfanilamide 7 c.c. intrathecally 115 c.c. subcutaneously 7 c.c. intrathecally 110 c.c. subcutaneously
	10-24-37	Rigidity less marked	101.8°	Slightly cloudy	Sterile	55 grains orally
	10-25-37	Generally better	99.8°			30 grains orally
	10-26-37	Improving	99.4°			35 grains orally
	10-27-37	Practically well	99.4°			No medication
	11- 3-37	No complaints	98.8°	10 cells		No medication
	11- 7-37	Discharged				
Recovered						
No. 2— M. P. 59 yrs. male	4- 3-38 3rd day of disease	Headache Vomiting				0.8% Sulfanilamide
	4- 4-38	Restless Toxic Confused Myringotomy. Moderate nuchal rigidity	100.0° 102.6° 105.2°	Cloudy 3900 cells	<i>Streptococcus viridans</i>	25 c.c. intrathecally 25 c.c. intravenously 75 c.c. subcutaneously 25 c.c. intrathecally 100 c.c. subcutaneously 100 c.c. intravenously 100 c.c. intravenously 100 c.c. intravenously
	4- 5-38	Delirious Extremely restless. Died 36 hrs. after admission	104.2°			100 c.c. intravenously 100 c.c. intravenously
Died						

Pneumococcic Meningitis. Pneumococcic meningitis is slightly more common than streptococcic meningitis¹⁴ but certainly there have been fewer attempts to treat it with sulfanilamide than the streptococcic form. Its high fatality may be judged by Tripoli's⁴ paper in which he reports 111 cases with but one recovery. Mertins and Mertins¹⁶ in surveying the literature of the past 15 years found only 31 cases in which recovery followed various procedures advocated by the respective authors. These authors

report a case of recovery following sulfanilamide therapy: the actual type was not determined although marked Type 4. Caldwell and Byrne¹⁷ cite a Type 1 case successfully treated with the drug. The typing was done by the precipitin and not by the Neufeld capsule method, as cultures were sterile. Mitchell and Trachsler¹⁸ report a case of Type 5 pneumococcic meningitis recovering after the use of optochin and sulfanilamide. They are inclined to give the credit to the optochin. Basman and Perley¹⁹ report three cases treated with sulfanilamide. Two, one a Type 3, the other untyped, died. The third, a Type 5, recovered. Applebaum¹¹ reports 32 cases treated with the drug, of which four recovered. The predominating types were 1 and 3. We had one case, a Type 27, with complete recovery after sulfanilamide (table 3). None of the recovered cases received anti-pneumococcus serum;

TABLE III
Pneumococcus Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— E. B. 11 yrs. male	8-17-37 3rd? day of disease	Headache, vomiting, lateral nystagmus	103.0°	Cloudy	Pneumococcus Type 27	0.8% Sulfanilamide 15 c.c. intrathecally 230 c.c. subcutaneously 15 c.c. intrathecally 110 c.c. subcutaneously
	8-18-37	Same	104.0°	Cloudy		11 c.c. intrathecally 110 c.c. subcutaneously 15 c.c. intrathecally 110 c.c. subcutaneously
	8-19-37	Clinically better	101.4°	Opalescent 380 cells		14 c.c. intrathecally 75 grains orally
	8-23-37	Improving	97.4°	65 cells	Sterile	9 c.c. intrathecally
	8-29-37	Drowsy	100.2°	26 cells		60 grains orally since 8-27-37
	9- 5-37	Fully recovered				
Recovered						

some received a few preliminary doses of antimeningococcic serum. There were three examples of meningitis due to Type 3 pneumococcus. All of these died in spite of the fact that Type 3 infection other than meningeal has reacted rather encouragingly to sulfanilamide. The total number of cases treated with sulfanilamide is 39 of which 30 or 76 per cent died, a high mortality but less than without it.

Influenzal Meningitis. Fothergill²⁰ found the mortality in untreated cases of influenzal meningitis about 98 per cent. Among 201 serum-treated cases, including series of Silverthorne, Fraser and Snelling²¹ and Schwentker,²² the mortality was 84.6 per cent. Silverthorne, Fraser and Snelling²¹ also report a mortality of 98 per cent in 70 untreated cases but the mortality in 36 serum-treated cases was only 72 per cent.

Of 18 cases of influenzal meningitis treated by sulfanilamide, Apple-

baum¹¹ reports but one recovery. We found five other cases in the literature,^{23, 24, 25, 19} all of which died. Both of our cases (table 4) succumbed. The one recovery received both anti-influenzal serum and sulfanilamide (prontosil and sulfanilamide), and Neal¹⁰ emphasizes this point, citing Provitzky's experiments on mice in which a combination of serum and sulfanilamide had a curative effect in otherwise fatal inoculations. Three other cases received both serum and sulfanilamide but ended fatally. The

TABLE IV
Influenzal Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bac- teriology	
No. 1— S. T. 11 mon. female	12-14-37 6th? day of disease	Marked nuchal rigidity, listless, hydrocephalus	103.2°	1600 cells	<i>H. influenzae</i>	0.8% Sulfanilamide
	12-15-37	Strabismus, more listless	103.2°	Purulent	<i>H. influenzae</i>	125 c.c. subcutaneously 175 c.c. subcutaneously
	12-16-37	Cephalic cry	103.0°	1000 cells 90 c.c. ventricular	<i>H. influenzae</i>	20 c.c. intraventricularly 10 c.c. intrathecally 125 c.c. subcutaneously 95 c.c. subcutaneously
	12-18-37		104.0°	50 c.c. ventricular 400 cells	<i>H. influenzae</i>	20 c.c. ventricularly 10 c.c. intrathecally 90 c.c. subcutaneously
	12-19-37	Stuporous	103.4°	200 cells	<i>H. influenzae</i>	15 c.c. intraventricularly 10 c.c. intracisternally 5 c.c. thoracic spine 5 c.c. lumbar spine
	12-20-37	Died Autopsy—Purulent meningitis. Internal hydrocephalus.				
No. 2— B. J. F. 3 mon. female	2-22-38 5th? day of disease	Listless, moderate nuchal rigidity	104.6°	Purulent	<i>H. influenzae</i>	10 c.c. 2.5% Prontosil subcutaneously
	2-23-38	Twitching of muscles	104.4°	Purulent	<i>H. influenzae</i>	0.8% Sulfanilamide 15 c.c. intrathecally 110 c.c. subcutaneously 20 c.c. Prontosil subcutaneously
	2-24-38	Marked nuchal rigidity	104.4°	Purulent	<i>H. influenzae</i>	15 c.c. intrathecally 110 c.c. subcutaneously 125 c.c. subcutaneously
	2-25-38	Condition unchanged	104.0°	Purulent	<i>H. influenzae</i>	15 c.c. intrathecally 110 c.c. subcutaneously 15 c.c. intrathecally 110 c.c. subcutaneously
	2-26-38		104.6°	Cloudy		10 c.c. intrathecally 115 c.c. subcutaneously
	2-27-38	Cyanotic at times	104.0°	Cloudy		20 c.c. intracisternally 105 c.c. subcutaneously
	2-28-38	Condition critical	104.6°			
	3- 1-38		101.0°			
	3- 2-38	Died				

results with sulfanilamide therapy in influenzal meningitis with or without serum so far, therefore, are not encouraging, there being 24 deaths in 25 cases, a mortality of 96 per cent. This is in contrast to the purely serum treated cases cited above.

Tuberculous Meningitis. The case of tuberculous meningitis herewith (table 5) reported was brought to the hospital in a critical condition and

TABLE V
Tuberculous Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— C. H. 19 mon. male	3-1-38 8th? day of disease	Stuporous. Moderate nuchal rigidity. Positive Kernig	101.0°	Opalescent 375 cells lymphocytic	Direct smear negative. Culture on ordinary media sterile	20 c.c. 2.5% Prontosil intramuscularly.
	3-2-38	Marked rigidity	102.0°	Opalescent	Sterile	0.8% Sulfanilamide 10 c.c. intrathecally 235 c.c. subcutaneously
	3-3-38	Condition grave. Died	104.6°			125 c.c. subcutaneously
		Autopsy report: Tuberculous meningitis. Mediastinal lymph node and pulmonary tuberculosis			4-2 tubercle bacillus on Petrognani medium (Cowen and Henderson modification)	
Died						

survived only 48 hours, during which time she was treated with intrathecal and subcutaneous doses of prontosil and sulfanilamide. A pure culture of the tubercle bacillus was obtained from the spinal fluid on Petrognani medium and the necropsy revealed tuberculous meningitis as well as pulmonary and lymph node involvement. We were unable to find in the literature any case treated with the drug. Rich and Follis,²⁶ however, in experimental tuberculosis in the guinea pig found that sulfanilamide exerted a striking inhibitory effect upon the development of lesions as compared with controls.

Meningitis of Undetermined Origin. The first of these two cases (table 6) in which we were unable to demonstrate the causal organisms was an adult whose history suggested a streptococcus infection following a tonsil operation. He was critically ill with meningitis when admitted to the St. Luke's hospital and lived but four days, during which time his spinal fluid was densely cloudy with very numerous polynuclears but no demonstrable bacteria, although the fluid was examined carefully and cultured daily on various media. The second case was a mild type in a child and lymphocytic choriomeningitis was considered, but the polynuclears were definitely predominant on all occasions. Here repeated spread examinations

and cultures were all negative. Cultures for tubercle bacilli and guinea pig inoculations were also negative. Recovery was complete and uncomplicated.

Cases like these are not very uncommon. Tripoli⁴ among 468 patients had 26 or 5 per cent of cases of purulent meningitis in which the type of organism was not reported. One of Schwentker's²⁷ cases of meningitis

TABLE VI
Undetermined Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— A. P. F. 30 yrs. male	7-10-37 4th day of disease	Stuporous severe headache	103.0°	Purulent	Smear and culture negative	0.8% Sulfanilamide 20 c.c. intrathecally 355 c.c. subcutaneously
	7-11-37	Marked nuchal rigidity	104.0°	Purulent	Smear	250 c.c. subcutaneously 55 c.c. intrathecally 250 c.c. subcutaneously
	7-12-37	Condition grave	108.0°	Cloudy yellow, 10,000 cells polynuclears	Smears and cultures nega- tive. Anaer- obic cultures not made	35 c.c. intrathecally 30 c.c. intrathecally 150 c.c. subcutaneously Blood transfusion 400 c.c.
	7-13-37	Died				
No. 2— T. W. 10 yrs. male	12- 1-37	Nuchal rigid- ity. Positive Kernig	104.0°	Opalescent 104 cells	Sterile	0.8% Sulfanilamide
	12-14-37	Photophobia. Blood culture sterile	104.8°			30 grains orally
	12-15-37	Restless, con- dition poor	104.0°	465 cells 75% polynuclears	Smear and culture nega- tive. Guinea pig inocula- tion negative (2-2-38)	10 c.c. intrathecally 115 c.c. subcutaneously 15 c.c. intrathecally 110 c.c. subcutaneously 15 grains orally
	12-16-37	Delirious	103.2°		Sterile	Same as 12-15
	12-17-37	Somewhat improved	100.2°	70 cells	Sterile for tu- bercle bacillus 3 weeks later on Petrognani medium, Cowen and Henderson modification	20 c.c. intrathecally 105 c.c. subcutaneously 15 grains orally
	12-18-37	Less irritable	102.0°			10 c.c. intrathecally 115 c.c. subcutaneously 10 c.c. intrathecally 115 c.c. subcutaneously 15 grains orally
	12-22-37	Improved	100.4°	60 cells	Sterile	From 12-19 to 12-22, re- ceived one-half the dose of 12-18
	12-26-37	Rigidity absent	99.4°			No medication
	12-30-37	Mantoux test (1:100) negative	99.4°			
	1- 7-38	Clinically negative	98.8°			
	1-14-38	Discharged				

was diagnosed meningococcic on a clinical basis, the organism not being demonstrable. We had a case of densely purulent meningitis following immediately upon a pneumonia and clinically pneumococcic meningitis. The most careful bacteriological examinations failed to reveal any bacteria.

Of several possible explanations, one is that, in the sulfanilamide cases, the organisms were missed in the primary examination and that later the sulfanilamide had sterilized the fluid. Another, perhaps more likely, is that the organisms were anaerobic. McDonald,²⁸ in discussing the rôle of anaerobic streptococci in human infections, cites four cases of meningitis in which anaerobic streptococci were isolated from the meninges at autopsy. F. W. Smith²⁹ recently reported a case of meningitis successfully treated with sulfanilamide, in which an anaerobic beta hemolytic streptococcus was isolated. This organism failed repeatedly to grow aerobically. We did not make definite anaerobic cultures in our cases and may have missed the causative organism this way. Smith's case, however, showed micrococci in the spread, whereas ours showed none at any time.

Meningococcus Meningitis. The mortality for meningococcus meningitis of course varies for different years and different locations. The United States Public Health Reports³⁰ for 1934 and 1935 list 6650 cases with a fatality of 53.2 per cent. Presumably most of these and likewise the cases which follow were serum treated. Tripoli⁴ found the mortality in the New Orleans Charity Hospital for the period 1925-1934 was 65.15 per cent. The Memphis³¹ fatality rate for 537 cases in the period 1925-1933 was 52.1 per cent. Levy³¹ in 176 patients treated with meningococcus antitoxin had a mortality of 34.6 per cent. In 135 of his patients ranging in age from one to 30 years, the mortality was 23.8 per cent. Hoyne³² reported 96 patients serum treated exclusively by the intravenous route with a mortality of 15.9 per cent.

Of cases treated with sulfanilamide, Schwentker³³ reports 52 patients with a mortality of 15.4 per cent. He compares these results with those attained in 278 consecutive patients treated with antimeningococcus serum in the same institution in the months immediately preceding the introduction of sulfanilamide therapy. In these the mortality was 30 per cent. In 24 other cases^{23, 18, 34, 19, 35, 36, 10, 37} there was only one death, a mortality of 4.2 per cent. Our own cases amount to eight and of these two died, a mortality of 25 per cent. The total is 84 cases with 11 deaths, a mortality of 13 per cent. A number of these cases received both serum and sulfanilamide, which clouds the issue as to the merit of sulfanilamide alone. Carey's³⁵ results are rather noteworthy. His five patients received sulfanilamide and no serum and all recovered, and furthermore only one received sulfanilamide intrathecally. Three had blood stream infections and two of these were given sulfanilamide intravenously with apparently good results.

TABLE VII
Meningococcic Meningitis

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 1— R. V. 10 yrs. male	6- 4-37 4th day of disease	Delirious. Nuchal rigidity. Photophobia	102.4°	Cloudy	Meningococcus	0.8% Sulfanilamide 15 c.c. intrathecally 110 c.c. subcutaneously
	6- 5-37	Rational	99.8°	Cloudy	Meningococcus	10 c.c. intrathecally 115 c.c. subcutaneously 20 c.c. intrathecally 105 c.c. subcutaneously
	6- 6-37	Nuchal rigidity marked	102.4°	Cloudy	Sterile	20 c.c. intrathecally 105 c.c. subcutaneously
	6- 7-37		102.2°	Cloudy	Sterile	10 c.c. intrathecally 90 c.c. subcutaneously
	6- 8-37	Improved	101.6°	Opalescent		8 c.c. intrathecally 70 c.c. subcutaneously
	6-14-37	Greatly improved	99.4°			80 c.c. subcutaneously on 6-9-, 100 c.c. on 6-10. 25 grains daily since 6-11
	6-19-37	Discharged				
No. 2— D. N. 15 yrs. female	6- 2-37 2nd day of disease	Unconscious. Nuchal rigidity	102.6°	Cloudy 19,900 cells	Meningococcus	0.8% Sulfanilamide 30 c.c. intrathecally 300 c.c. subcutaneously
	6- 3-37	Rational	100.6°	Cloudy	Meningococcus	25 c.c. intrathecally 225 c.c. subcutaneously
	6- 4-37	Improved	99.6°	Slightly cloudy	Sterile	25 c.c. intrathecally 225 c.c. subcutaneously 125 c.c. subcutaneously
	6- 5-37		100.6°	Opalescent	Sterile	15 c.c. intrathecally 110 c.c. subcutaneously 125 c.c. subcutaneously
	6-10-37	No complaint	98.6°	Clear	Sterile	95 c.c. subcutaneously on 6-6 and 150 c.c. on 6-7
	6-19-37	Discharged	98.4°			40 grains daily from 6-8 to 6-14
No. 3— R. V. A. 5 yrs. male	12-22-37 3rd day of disease	Comatose. Marked nuchal rigidity. Petechiae. Critical	105.0° 106.0° 107.0°	Cloudy 4,900 cells Cloudy	Meningococcus	0.8% Sulfanilamide 12 c.c. intrathecally 110 c.c. subcutaneously 10 c.c. intrathecally 115 c.c. subcutaneously
	12-23-37 6 a.m. 6:30 a.m.	Moribund Died	108.0°			
Died						

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 4— C. W. 13 mon. female	1-31-38 4th day of disease	Photophobia irritable strabismus. Positive Kernig. Nuchal rigidity	104.0°	Purulent	Meningococcus	10 grains Sulfanilamide orally
	2- 1-38		103.4°	23,000 cells	Meningococcus	0.8% Sulfanilamide 25 c.c. intrathecally 10 c.c. intrathecally 10 grains orally
	2- 2-38	Blood culture sterile	100.4°	Cloudy	Sterile	5 c.c. intrathecally 10 grains orally
	2- 4-38	Improved	100.4°			10 grains daily orally
	2-10-38	Greatly improved	99.0°	153 cells	Sterile	6 grains daily since 2-4 orally
	2-15-38	Fully recovered		27 cells		
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No. 5— C. L. 21 yrs. male	2- 2-38 4th day of disease	Stuporous. Moderate nuchal rigidity	102.0°	280 cells (50% polynuclears)	Meningococcus	40 grains Sulfanilamide orally
	2- 3-38	Lower extremities spastic	105.0°	150 cells	Meningococcus	Antimeningococcic serum 20 c.c. intrathecally 20 c.c. intravenously 60 grains Sulfanilamide orally
	2- 4-38	Condition unchanged	106.0°	Cloudy	Meningococcus	Same as on 2-3
	2- 5-38	Somewhat improved	104.0°	Slightly cloudy	Sterile	Antimeningococcic serum 10 c.c. intrathecally 10 c.c. intravenously 60 grains Sulfanilamide orally
	2- 6-38	Improvement continues. Less rigidity	102.0°	Slightly cloudy	Sterile	Same as on 2-5
	2- 7-38		100.0°	Slightly cloudy		60 grains Sulfanilamide orally
	2- 8-38	Generally improved	99.0°			30 grains Sulfanilamide orally
	2-10-38					Same since 2-8
	2-11-38	Rash, wakeful, probably due to drug	102.0°			Medication stopped
	3-23-38	Patient has been well since 2-13. Residual spasticity has disappeared				
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Recovered						

TABLE VII (Continued)

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 6— H. B. 12 yrs. male	2-15-38 2nd day of disease	Stuporous. Nystagmus. Nuchal rigidity	103.8°	Purulent	Meningo- coccus	0.8% Sulfanilamide 9 c.c. intrathecally 116 c.c. subcutaneously
	2-16-38	Blood culture sterile	106.6°	Purulent	Meningo- coccus	12 c.c. intrathecally 6 c.c. intrathecally 55 grains orally
	2-17-38	Rational	101.0°	Cloudy 1065 cells	Sterile	12 c.c. intrathecally 45 grains orally
	2-19-38	Greatly improved	100.4°	Cloudy	Sterile	30 grains orally
	2-22-38		100.2°	245 cells	Sterile	Same since 2-19
	2-27-38	Fully recovered				No medication since 2-22-38
No. 7— T. L. 15 mon. male	3-14-38 3rd day of disease	Listless. Nu- chal rigidity. Kernig, bulg- ing fontanelle	102.0°	8,500 cells	Meningo- coccus	10 c.c. intrathecally 115 c.c. subcutaneously 20 c.c. 2.5% Prontosil
	3-15-38		102.6°	Cloudy	Meningo- coccus	10 c.c. intrathecally 115 c.c. subcutaneously 10 c.c. intrathecally 115 c.c. subcutaneously
	3-16-38	Improving	100.0°	Slightly cloudy	Sterile	10 c.c. intrathecally 115 c.c. subcutaneously
	3-17-38		100.0°	Same	Sterile	Same as on 3-15.
	3-18-38	Takes food	101.6°	Opalescent	Sterile	125 c.c. subcutaneously
	3-20-38	Alert	101.0°			125 c.c. subcutaneously 3-20 40 c.c. 2.5% Prontosil 3-19
	3-25-38	Improved	100.0°	27 cells	Sterile	15 grains orally from 3-19
	3-31-38	Fully recovered	98.6°			10 grains orally since 3-25

TABLE VII (Continued)

Case	Date	Symptoms		Spinal Fluid		Treatment
		Status of Patient	Temperature	Appearance Cell Count	Bacteriology	
No. 8— L. A. 42 yrs. female	3-24-38 3rd day of disease	Severe headache. Positive Kernig. Nuchal rigidity absent	100.0°	Purulent	Meningococcus Type I	0.8% Sulfanilamide 30 c.c. intrathecally 175 c.c. subcutaneously 75 gr. orally 40 c.c. 2.5% Protosil intramuscularly
	3-25-38	Mentally confused	98.4°	Cloudy 3000 cells	Sterile	15 c.c. intrathecally 110 c.c. subcutaneously 75 gr. orally
	3-29-38	Some improvement	100.0°	Gradual reduction to 120 cells	Sterile since 3-25	Same since 3-25
	4- 2-38	Marked improvement in last 3 days. Slight headache today	101.8°	440 cells	Few meningococci	50 grains orally since 3-30
	4- 5-38	Slight nuchal rigidity. Toxic	103.8°	4345 cells	Meningococci	20 c.c. intrathecally 180 c.c. subcutaneously 70 gr. orally since 4-3
	4- 6-38	Same	104.4°	2400 cells	Sterile	Same as 4-5
	4- 7-38	Unchanged. Blood culture sterile	101.2°	332 cells	Sterile	15 c.c. intrathecally 185 c.c. subcutaneously 75 gr. orally
	4- 9-38	Severe anemia	103.0°	2800 cells 2600 cells	Sterile meningococcus	Same since 4-7. Blood transfusion 500 c.c.
	4-10-38	Slightly better	103.6°	Yellow 2400 cells	Meningococcus	Sulfanilamide as above. Antimeningococcic serum 27 c.c. intrathecally 33 c.c. intravenously
	4-11-38	Rigidity more marked	103.4°	4500 cells	Meningococcus	90 gr. Sulfan. orally Meningococcic antitoxin 25 c.c. intrathecally 35 c.c. intravenously
	4-14-38	Generally worse	102.2°	2700 cells	Meningococcus	Therapy same since 4-11
	4-18-38	Stuporous, severe headache Marked nuchal rigidity. Chill	105.0°			Therapy same except that antimeningococcic serum substituted for antitoxin, intraven.
	4-19-38	Projectile vomiting. Involuntaries	103.0°	415 cells	Meningococcus	25 c.c. Sulfan. intrathec. 475 c.c. subcutaneously 30 c.c. serum intraven.
	4-20-38	Condition grave. Blood culture sterile	103.6°	841 cells	Meningococcus	30 c.c. serum intrathec. 45 gr. Sulfan. orally Blood transfusion 300 c.c.
	4-21-38	Died one month from onset of illness				Note—antimeningococcic serum agglutinated the organisms in dilution of 1 : 800

Six of our eight cases were treated with sulfanilamide alone with one death. One case which recovered was an infant of 15 months who inadvertently received sulfanilamide for six weeks daily without untoward effects. In one of the two cases treated with both sulfanilamide and serum, the drug was at first used with seemingly excellent results, the spinal fluid becoming sterile in 48 hours and the cells dropping from 2470 to 120 with

marked clinical improvement. Though treatment was continued, the patient after about a week relapsed, the cells rose to the thousands and meningococci were again found in smear and culture. With no improvement, antitoxic and antimeningococcic sera were used in large quantities along with sulfanilamide, but the meningococci persisted and after a month's illness, the patient succumbed. The organism was a typical Type 1 meningococcus and it was agglutinated by the antimeningococcus serum used in a dilution of 1:800. In the second case treated with both sulfanilamide and serum, the patient recovered but suffered during convalescence with weakness in one leg and incontinence of urine.

In experimental work upon mice, Brown³⁸ found that the protective influence of 8 mg. of sulfanilamide is comparable to that of 0.1 c.c. of high grade antimeningococcus serum. He also found that the combination of sulfanilamide and serum produced a greater degree of protection than either agent by itself, confirming similar experiments of Branham and Rosenthal.³⁹ Neter⁴⁰ found that sulfanilamide markedly inhibited the growth of meningococci in spinal fluid obtained from patients with meningococcus meningitis.

Altogether, the clinical results in meningococcic meningitis are encouraging but not startling. Patients treated with both serum and sulfanilamide did not seem to do better than those treated with sulfanilamide alone. Nor did treatment with serum alone seem superior to sulfanilamide alone. Other things being equal, sulfanilamide is naturally preferable on the grounds of economy and the absence of serum disease.

Gonococcic Meningitis. Marvin and Wilkinson⁴¹ report a case of gonococcic meningitis first diagnosed meningococcic and treated with antimeningococcus serum. Later with the correct diagnosis sulfanilamide was used. The patient recovered, but the authors are not inclined to give sulfanilamide the credit. The mortality for 22 cases in the literature, not treated with sulfanilamide, was 45 per cent.

Bacillus Proteus Meningitis. Basman and Perley¹⁹ report a case of *Bacillus proteus* meningitis in which the organism was recovered from the blood and the spinal fluid. The patient responded well to sulfanilamide but finally required a mastoidectomy. *Bacillus proteus* was cultured from the mastoid wound. The child made a complete recovery.

DISCUSSION

This survey of various types of meningitis treated with sulfanilamide includes 205 cases from the literature and 22 cases of our own (table 8), a total of 227. The matter is viewed here almost solely as a clinical experiment analogous to experimental work in animals in which the death or survival of the animal is the criterion of the success or failure of the therapeutic experiment. This is feasible because of the almost certain

fatal outcome of all forms of acute meningitis, so that recovery under sulfanilamide of any large group of cases may be reasonably attributed to the drug. Exceptions are taken in meningococcic and gonococcic meningitis in which the mortality with or without other treatment is much lower,

TABLE VIII
Cases of Meningitis Treated with Sulfanilamide

Organism	Number	Recovered	Died
<i>Streptococcus hemolyticus</i>	6	4	2
<i>Streptococcus viridans</i>	2	1	1
<i>Pneumococcus</i>	1	1	0
<i>H. influenzae</i>	2	0	2
<i>Mycobacterium tuberculosis</i>	1	0	1
<i>Neisseria intracellularis</i>	8	6	2
Undetermined	2	1	1
Total	22	13	9

and here conclusions as to the therapeutic worth of the drug must be correspondingly modified.

It is evident at once that no conclusions can be drawn as to the value of sulfanilamide in meningitis as an entity on account of the variation in results in the different types of meningeal infection. Nor can final opinions be given in most instances as to the individual forms of infection until more cases accumulate in the literature. This paper is in part a contribution to that end. It may be said, however, that the value of sulfanilamide in beta hemolytic streptococcus meningitis has been established beyond dispute. A reduction of the mortality from 95 per cent and above to about 20 per cent speaks for itself. Sulfanilamide treated infections due to *Streptococcus viridans*, the tubercle bacillus, or the gonococcus are too few in number for appraisal. The results so far in influenzal meningeal infections are very discouraging. In pneumococcic meningitis with its terrific mortality, the outcome, nine recoveries in 39 cases, at least warrants further trial and seems to offer possibilities. In meningococcic meningitis we collected 84 cases with 11 deaths, a mortality of only 13 per cent, which appears remarkable. Hoyne,³² however, reports only 16 per cent mortality in serum treated cases, and as many of the drug cases also received serum, conclusions should be withheld. As pointed out, if results are equal, sulfanilamide seems preferable.

The experimental work to determine the mode of action of sulfanilamide has emphasized some factors which may have clinical application. Sulfanilamide has little bactericidal effect in vitro⁴² when added to broth cul-

tures of streptococcus. Lockwood⁴³ found, however, that sulfanilamide in a concentration found in patients receiving the drug will prevent the multiplication of streptococci in cell free normal human serum. And Hoare⁴⁴ states that a considerable bactericidal power was demonstrated in normal human serum to which sulfanilamide has been added in vitro. Osgood³ found in marrow culture experiments with sulfanilamide and streptococci that the drug "did not appear to kill the organisms directly, although it does permit the bactericidal properties of human serum and to some extent phagocytosis by leukocytes to kill organisms which they would otherwise be unable to kill." Brown³⁸ in experimental meningococcus infection found that the combination of sulfanilamide and antimeningococcus serum produced more protection than either agent by itself or by a combination of sulfanilamide and a non-specific serum such as antipneumococcus serum. Branham and Rosenthal³⁹ noted the superiority of combined drug (sulfanilamide) and serum therapy in mice infected with Type 1 pneumococcus. If this serum factor is important in sulfanilamide therapy, then clinically one would expect the best results when a specific antiserum was administered along with the drug. As a matter of fact, this was often done in meningococcus meningitis in which both serum and drug were used, but it cannot be said that the results were more impressive than with the drug alone. Likewise in influenzal meningitis, the cases in which both anti-influenzal serum and sulfanilamide were used did not show noteworthy results. On the other hand, in beta hemolytic streptococcus meningitis in which the very best results were obtained, antiserum was not used. Although in all clinical cases the serum factor may be conceived as playing a participating and perhaps important rôle, the necessity for specific serums in addition to the drug, as suggested by experimental work, has yet to be proved.

The matter of intrathecal treatment with sulfanilamide in these infections might be worthy of comment. There seems to be a tendency in diseases like meningococcus meningitis and tetanus to do away with or minimize intraspinal serum administration with apparently improving results. Of 15 meningococcic patients of Hoyne's⁴⁵ treated intravenously with serum and without any lumbar puncture, only one died. Hoyne³² thinks the intrathecal method of serum therapy prolongs the recovery of the patient. As satisfactory blood and spinal fluid concentrations of sulfanilamide are easily attained by the oral route, it might be better to do away with intrathecal treatment and avoid the possible irritating influence of spinal taps for drainage and injection purposes. Our own tendency would be to minimize intraspinal work.

SUMMARY

This paper is a survey of 227 cases of infectious meningitis, including 22 of our own, treated with sulfanilamide. The results in the various types

of infection are discussed and the part which the simultaneous use of antiserum may play is considered.

ADDENDUM

Since the above paper was submitted, there have been numerous reports of various types of meningitis treated by the sulfonamide group of drugs, particularly the new sulfapyridine.

Toomey and Kimball⁴⁶ report a mortality of 16.6 per cent in 12 cases of hemolytic streptococcus meningitis treated with sulfanilamide. They collected 98 cases, including a number mentioned in our paper, with a mortality of 18 per cent. This is about the same death rate we found with this organism. The figures of Long and Bliss⁴⁷ for hemolytic streptococcus meningitis under the sulfonamide treatment are higher, a mortality rate of 35 per cent.

Results in the treatment of pneumococcic meningitis seem much improved. Allan, Mayer and Williams⁴⁸ report three cases of pneumococcic meningitis in which sulfanilamide was given but no specific antipneumococcic serum. All recovered. Finland, Brown and Rauh⁴⁹ report six recoveries in 10 cases of pneumococcic meningitis. We treated with sulfanilamide and sulfapyridine a type 18 pneumococcic meningitis in an infant of six months. The patient died. MacKeith and Oppenheimer⁵⁰ report two recoveries out of five cases of pneumococcic meningitis treated with sulfapyridine. Hewell and Mitchell⁵¹ obtained four recoveries out of seven cases of pneumococcic meningitis treated with sulfanilamide or related compounds and contrast this with their 100 per cent fatalities in 23 cases before the sulfanilamide era.

We have further treated three cases of influenzal meningitis with sulfanilamide and sulfapyridine combined with serum. There was one recovery. Our impression of the drugs' value was unfavorable.

Branham, Mitchell and Brainin⁵² report a recovery in a case of gonococcic meningitis under sulfanilamide.

Folsom and Gerchow⁵³ (quoted by Long and Bliss) report the unsuccessful treatment of a case of meningitis due to Friedlander's bacillus.

Contributions on meningococcic meningitis are very encouraging. Banks⁵⁴ obtained 15 recoveries in 16 cases treated with sulfanilamide alone. This 6 per cent fatality rate contrasts with 11.8 per cent deaths in 59 cases in which both sulfanilamide and serum were used and 16 per cent mortality with serum alone. Waghelstein⁵⁵ likewise had better results with sulfanilamide alone than with combined drug and serum therapy. In 72 adequately treated cases, using the drug only, there was a death rate of 11.59 per cent which, however, is not strikingly lower than his mortality of 16.71 per cent in a large group treated with serum only. Muraz, Chirle and Queguiner⁵⁶ (quoted by Long and Bliss) in an epidemic of meningococcic meningitis among natives of French Nigeria had only 10.7 per cent fatalities in 271 patients treated with sulfanilamide alone, 8.7 per cent deaths when using a combination of serum and sulfanilamide in 23 patients and 14.8 per cent deaths when employing intrathecal injections along with sulfanilamide by mouth. They contrast this with 74.6 per cent deaths in 8,653 patients afflicted with the disease in the presulfanilamide days. In the Anglo-Egyptian Sudan, where conditions are very unfavorable and the mortality usually from 65 to 70 per cent, Somers⁵⁷ treated 143 consecutive cases with sulfapyridine, with a mortality of 10 per cent. In the same district, Bryant and Fairman⁵⁸ treated 21 cases with sulfanilamide and 168 patients with sulfapyridine. The death rate in both series was but 5 per cent.

The trend of opinion as to the action of the sulfonamide drugs seems to be that there is some interference with bacterial metabolism or nutrition whereby bacterial growth is prevented or retarded, thus allowing the normal or immune defense mecha-

nism to handle the situation adequately.^{59, 60} In general, the tendency in meningitis treatment is to avoid intrathecal medication and spinal drainage or frequent spinal taps.^{46, 55}

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FIVE YEARS' EXPERIENCE (1933-1937) WITH MORTALITY FROM ACUTE CORONARY OCCLUSION IN PHILADELPHIA *

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OVER a quarter of a century has passed since Herrick¹ in 1912 directed the attention of the medical profession to the clinical diagnosis of acute coronary occlusion. Although a few men before Herrick had diagnosed this condition antemortem, he was the first to focus interest on this now well recognized clinical entity. In the words of Sir William Osler,² "In science the credit goes to the man who convinces the world, not to the man to whom the idea first occurs."

During the period since 1919³ studies have been made of this disease from nearly every conceivable point of view. Studies of mortality from coronary disease have consisted for the most part in attempts to reconstruct diagnoses made in the past to fit modern conceptions of this disease. This is the first attempt to analyze deaths reported as due to acute coronary occlusion in a large city over a period of several years.

During the period from January 1, 1933 to December 31, 1937, 5116 deaths were reported by physicians in Philadelphia as due to acute coronary occlusion, coronary thrombosis, and other practically synonymous terms. So far as was possible this study was limited to deaths apparently due to an acute coronary "accident," the result of coronary atherosclerosis. Deaths indicated as due to coronary sclerosis and other chronic degenerative diseases were excluded, as were also deaths certified as due to syphilitic involvement of the coronary arteries or to coronary embolus in rheumatic heart disease or subacute bacterial endocarditis.

Sources of Material. Of these 5116 deaths, 703, or 13.7 per cent, occurred among patients regularly admitted to 26 civilian hospitals approved for internship by the American Medical Association; 1868, or 36.5 per cent, were coroner's cases; and 2545, or 49.8 per cent, were reported from all other sources (table 1). Of these, 2440 deaths occurred in the homes, while 105 occurred in hospitals other than those mentioned. For practical purposes this group may be regarded as composed of deaths reported by practicing physicians. Of the deaths occurring in hospitals, 197 diagnoses were confirmed by postmortem findings.

The age distribution and mean ages at deaths from these three sources differed to a certain extent. Coroner's cases indicated the youngest age distribution, with a peak incidence in the 50-59 year age decade (figure 1).

* Read at the New Orleans meeting of the American College of Physicians March 28, 1939.

From the Office of Heart Disease Investigations. National Institute of Health, United States Public Health Service. Branch Office, 133 S. 36th St., Philadelphia, Pa.

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The mean age at death among coroner's cases was 58.1 years. Among all other groups studied the maximum number of deaths occurred in the 60-69 year age period. The mean age of deaths occurring among patients regularly admitted (exclusive of coroner's cases) to 26 civilian hospitals ap-

TABLE I

Number of Deaths Attributed to Acute Coronary Occlusion in Philadelphia Each Year from January 1, 1933 to December 31, 1937, among Patients Regularly Admitted to 26 Civilian Hospitals Approved for Internship by the American Medical Association, Coroner's Cases, Deaths Reported from All Other Sources, and the Total Number of Deaths Attributed to This Cause

Year	Deaths in Civilian Hospitals Approved for Internship by the American Medical Association	Coroner's Cases	Deaths in Other Hospitals and in the Homes	Total
1933	114	258	300	672
1934	96	299	408	803
1935	159	383	454	996
1936	140	403	581	1124
1937	194	525	802	1521
Total	703	1868	2545	5116
Percentage of total	13.7	36.5	49.8	100.0
Percentage increase in 5 years	70	103	167	126

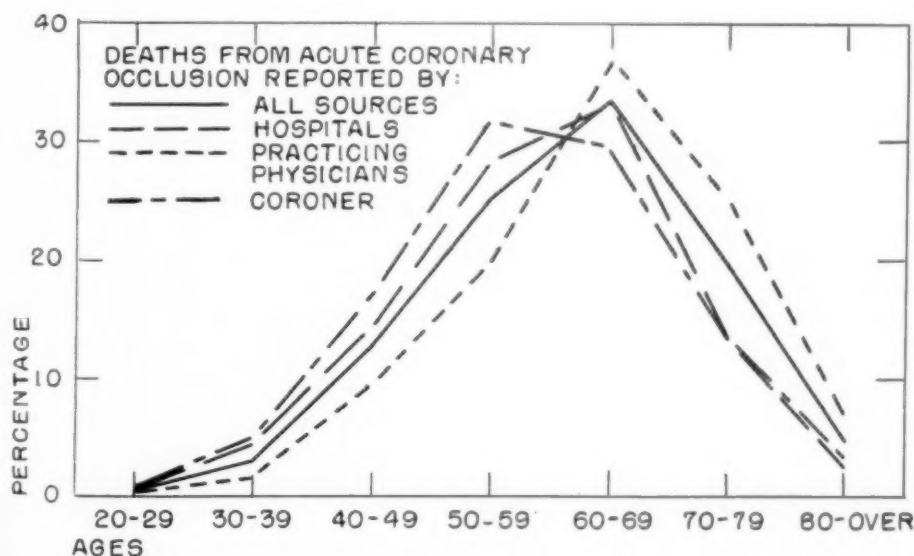


FIG. 1. Percentage age distribution by decades of life of 5116 deaths reported as due to acute coronary occlusion, 703 deaths reported from 26 civilian hospitals approved for internship by the American Medical Association, 1868 coroner's cases and 2545 deaths from other sources, most of which occurred in the homes, in Philadelphia from January 1, 1933 to December 31, 1937.

proved for internship by the American Medical Association was 59.5 years; among necropsied cases 59.8 years. The mean age of deaths attributed to this cause and occurring in the homes was 63.9 years. The mean age of the entire series of 5116 deaths was 62.1 years.

The fact that the mean ages at death of cases occurring in the homes was older by more than four years than deaths in hospitals was only to be expected. An even greater difference was noted among deaths from rheumatic heart disease.⁴ It occurs chiefly because elderly persons are not as frequently admitted to hospitals.

Accuracy of Diagnoses. While it is not possible for a statistical analyst reviewing a large series of cases to determine the accuracy of diagnosis in each fatal case, efforts should be made to compare the age distribution with that observed and reported from sources believed to be reliable. In figure 2

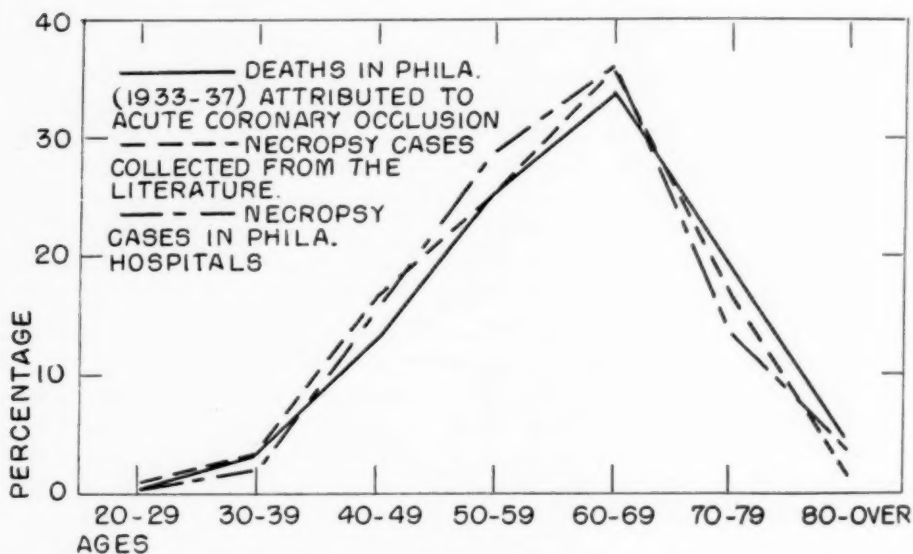


FIG. 2. Percentage age distribution, by decades of life, of 5116 deaths reported as due to acute coronary occlusion in Philadelphia from January 1, 1933 to December 31, 1937, compared with 284 necropsied cases collected from the literature and 197 fatal cases in this series in which the diagnoses were based on necropsy findings.

a comparison is made of these 5116 deaths with 197 deaths in hospitals, in which the diagnoses were confirmed by postmortem examinations and with 284 necropsy cases collected from the literature, consisting of the combined studies of Levine,⁵ Saphir et al.,⁶ Applebaum and Nicolson,⁷ and Meakins and Eakin.⁸ The age distribution of deaths reported as due to acute coronary occlusion in Philadelphia during these five years compares quite closely with the age distribution observed in these two series based on postmortem findings.

In figure 3 is shown the age distribution and mean ages at death during each year of the quinquennium under study. Despite an increase of 126

per cent in the total number of deaths reported in 1937 as compared with 1933, the age distribution is so nearly the same that the lines in this figure are nearly indistinguishable. The mean ages at death varied only 1.8 years during this period. As a corollary to this lack of variability in the age distribution, it seems apparent that the increase in reported mortality cannot be attributed to a tendency to report more deaths among very old persons as due to this cause.

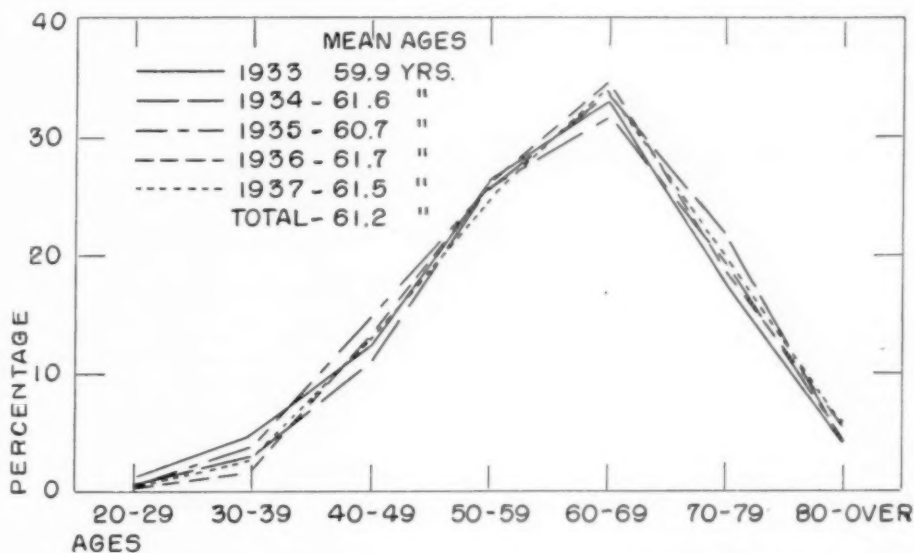


FIG. 3. Percentage age distribution, by decades of life, and mean ages at death of 5116 deaths reported as due to acute coronary occlusion in Philadelphia based on the number of deaths occurring in each of the five years under study.

This is further illustrated by a comparison of deaths attributed to acute coronary occlusion with deaths from all heart disease (table 2). In the age period 50-59 years 26.0 per cent of the deaths reported as due to heart disease were attributed to acute coronary occlusion. This percentage declines with each succeeding decade so that in the age period past 80 years of age only 5.5 per cent of all deaths from heart disease were reported as due to acute coronary occlusion. Furthermore, while the age specific death rates from all forms of heart disease increased precipitously in the age periods past 70 years of age, the age specific mortality rates from acute coronary occlusion showed a very gradual increase.

Of the total deaths attributed to this cause only 24.5 per cent occurred among persons past 70 years of age, while among deaths from all heart disease during this five-year period 42.1 per cent occurred among persons past 70 years of age. Of the deaths from coronary occlusion occurring in hospitals only 19.1 per cent occurred among persons over 70 years of age. Even among deaths occurring in the homes only 31.9 per cent were over

70 years of age. On the other hand, of the total deaths attributed to acute coronary occlusion, 41.1 per cent occurred among persons younger than 60 years of age. As depicted in the general mortality returns, acute coronary occlusion is primarily a problem of the 40-69 year age period.

In the opinion of the writer, acute coronary occlusion is not being used in Philadelphia as a blanket diagnosis of deaths among persons in advanced age periods. Although there were doubtless some incorrect diagnoses, the age distribution conforms quite closely to the accepted age distribution of this disease. For the most part, these diagnoses appeared to have been made with an attempt to portray a definite clinical condition.

TABLE II

Comparison of Number of Deaths and Age Specific Death Rates from Acute Coronary Occlusion with Reported Mortality from All Heart Disease in Philadelphia from January 1, 1933 to December 31, 1937 (Based on the U. S. Census of 1930)

Age Groups	Population	Deaths from Coronary Occlusion	Mean Annual Specific Death Rate per 100,000 Population	Deaths from All Forms of Heart Disease	Mean Annual Specific Death Rate per 100,000 Population	Percentage of Total Heart Disease Due to Acute Coronary Occlusion
20-29	356,592	21	1	483	27	4.3
30-39	333,058	160	10	1,100	66	14.5
40-49	259,787	663	51	2,817	217	23.5
50-59	181,963	1,299	143	4,992	549	26.0
60-69	108,545	1,720	317	8,492	1,565	20.3
70-79	44,083	1,003	455	8,508	3,860	11.8
80 and over	10,165	248	488	4,474	8,803	5.5
Total	1,294,193	5,114*		30,866		

* 2 ages unknown.

Race and Sex Distribution. These studies indicate a much lower mortality from acute coronary occlusion among Negroes as compared with white persons. The mean annual death rate was 56 per 100,000 white persons as compared with 21 per 100,000 Negroes. The lower mortality rate among Negroes is not entirely due to a younger age distribution of the colored population, since the mean annual age specific death rates by decades of life are lower among Negroes than among white persons (table 3). While this may be due in part to less accurate diagnoses of acute coronary occlusion among colored people, it is probably more than offset by the mis-diagnosis of more cases of syphilitic cardiovascular disease as acute coronary occlusion.

Only 231, or 4.5 per cent of the 5116 deaths reported as due to acute coronary occlusion occurred among colored persons (table 4). According to the U. S. Census of 1930, Negroes accounted for 11.3 per cent of the population of Philadelphia. Of the deaths from acute coronary occlusion among regularly admitted patients to 26 civilian hospitals approved for internship by the American Medical Association, only 5.7 per cent were

TABLE III

Number of Deaths and Mean Annual Age Specific Death Rates by Age Decades per 100,000 Population from Acute Coronary Occlusion According to Color of Decedents in Philadelphia for the Period from January 1, 1933 to December 31, 1937
(Based on the U. S. Census of 1930)

Age Decade (years)	Total—Both Races			White			Colored		
	Population	Deaths	Mean Annual Rate per 100,000	Population	Deaths	Mean Annual Rate per 100,000	Population	Deaths	Mean Annual Rate per 100,000
20-29.....	356,592	21	1	306,339	15	1	50,253	6	2
30-39.....	333,058	160	10	285,323	132	9	47,735	28	12
40-49.....	259,787	663	51	229,663	605	53	30,124	58	39
50-59.....	181,963	1299	143	167,316	1222	146	14,647	77	105
60-69.....	108,545	1720	317	103,446	1675	324	5,099	45	177
70-79.....	44,083	1003	455	43,429	990	467	1,654	13	157
80 and over.....	10,165	248	488	9,704	244	503	461	4	174
Total over age 20 yrs.....	1,294,193	5114*	79	1,144,220	4883	85	149,973	231	31

* 2 deaths with ages unknown.

TABLE IV

Number and Percentage of Deaths in Each Age Decade and Mean Age at Death According to Color and Sex among 5116 Deaths Attributed to Acute Coronary Occlusion in Philadelphia (from All Sources) from January 1, 1933 to December 31, 1937

Age Decade (years)	Total						White						Colored					
	Both Sexes		Male		Female		Both Sexes		Male		Female		Both Sexes		Male		Female	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
20-29.....	21	4	10	3	11	6	15	3	8	3	7	4	6	2.6	2	1.6	4	3.7
30-39.....	160	3.1	107	3.2	53	3.0	132	2.3	91	2.8	41	2.5	28	12.1	16	12.9	12	11.2
40-49.....	663	13.0	521	15.4	142	8.2	605	12.4	487	15.0	118	7.3	58	25.1	34	27.5	24	22.4
50-59.....	1299	25.4	952	28.2	347	20.0	1222	25.0	910	28.0	312	19.1	77	33.3	42	33.8	35	32.7
60-69.....	1720	33.6	1111	32.9	609	35.0	1675	34.3	1092	33.6	583	35.7	45	19.6	19	15.3	26	24.4
70-79.....	1003	19.6	566	16.8	437	25.1	990	20.3	556	17.0	434	26.6	13	5.6	10	8.1	3	2.8
80 and over.....	248	4.9	108	3.2	140	8.1	244	5.0	107	3.3	137	8.4	4	1.7	1	.8	3	2.8
Unknown....	2		2		0		2		2		0		0		0		0	
Total.....	5116	100	3377	100	1739	100	4885	100	3253	100	1632	100	231	100	124	100	107	100
Percentage of total...		100		66.0		34.0		95.5		63.6		31.9		4.5		2.4		2.1
Mean ages at death..	61.2		59.8		63.9		61.6		60.0		64.7		52.3		52.0		52.7	

among Negroes. This occurs despite the fact that due to their less fortunate economic status, Negroes account for a disproportionately large part of the hospital admissions for all causes.

Although coronary occlusion appeared to be less frequent among Negroes, the age distribution and mean ages indicated deaths at considerably younger ages. The mean age at death among white persons in the series

as a whole was 61.6 years as compared with 52.3 years among Negroes. Among the 703 deaths in hospitals, the mean age at death among white persons was 60.1 years as compared with 49.0 years among Negroes. The few necropsy cases among Negroes also supported this view.

Among deaths attributed to acute coronary occlusion from the city as a whole, the mean age among males was 59.8 years, as compared with 63.9 years among females, more than four years older than the males. Of the deaths in hospitals the mean age among males was 60.1 years as compared with 59.1 years among females. Since there is an element of selection of cases dying in hospitals, the mean ages at death in the entire city are probably more accurate. The age distribution also indicated deaths at younger ages among males.

The ratio of males to females was approximately 2 to 1. This is lower than has been reported in other series and may be due to relatively more females past 70 years of age. It is noteworthy, however, that of the deaths among patients regularly admitted to hospitals the ratio of males to females was only 1.7 to 1. Among the coroner's cases, however, the ratio was 3.6 to 1. Since over 95 per cent of the deaths attributed to this disease occurred among white persons, the ratio of deaths among males as compared with females was about the same as for the entire series. Among Negroes, however, there were nearly as many deaths among females as among males reported as due to this cause.

A more complete analysis of these 5116 deaths attributed to this cause, with tables giving detailed information concerning cases occurring in hospitals, in the homes, coroner's cases, and diagnoses confirmed by necropsy will be reported in another publication.⁹

Monthly Distribution. In general, the distribution of deaths from this cause by months corresponded to the monthly distribution of deaths from all heart disease and of deaths from all causes (figure 4). There were only 53 per cent as many deaths from acute coronary occlusion in August as in December. Although the seasonal variation in deaths from this cause is not as marked as in deaths from certain infectious diseases, the number of deaths was appreciably lower during the summer months.

Countries of Birth. The mean age at death was more advanced among persons born in Germany among whom it was 66.7 years and youngest among Italians among whom it was 57.2 years. Deaths among other foreign born persons ranged between these two extremes. Among native born white Americans the mean age at death was 61.7 years. The mean age at death among foreign born persons depended largely on the period in which the greatest amount of immigration occurred. Among foreign born persons from countries from which the immigration was the greatest prior to 1900, the mean ages at death indicated deaths at older age periods than among persons from countries from which immigration was largest subsequent to that time. It is doubtful if nationality plays an important rôle in determining the age at death.

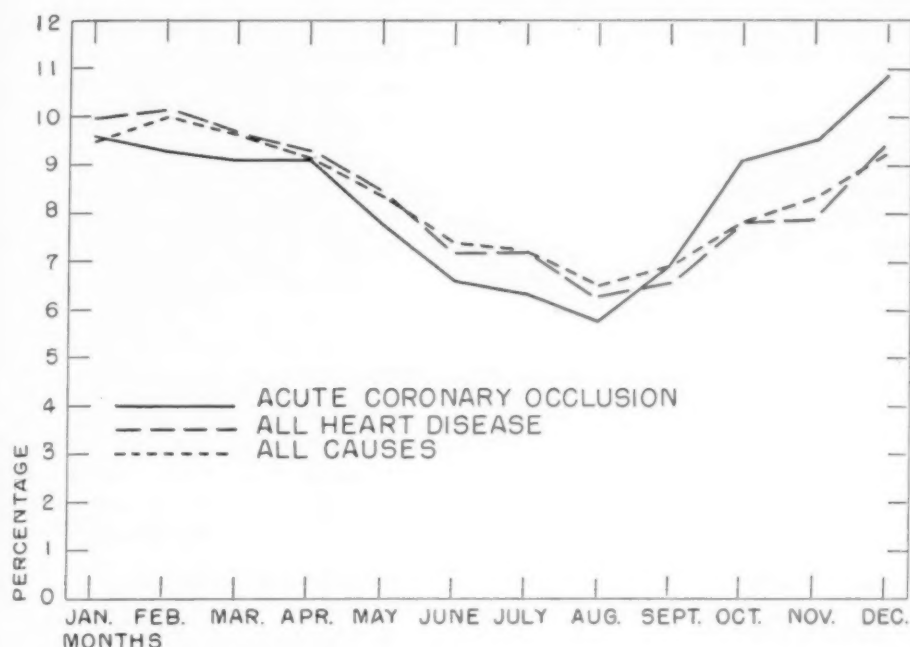


FIG. 4. Percentage distribution of deaths from acute coronary occlusion by months (adjusted to a 30-day basis) as compared with deaths from all causes and from all heart disease in Philadelphia from January 1, 1933 to December 31, 1937.

The age specific death rate according to nations of birth indicated considerably higher death rates among persons born in Russia and in Austria-Hungary than among persons born in other foreign countries or among native born white Americans (table 5). This was especially notable in the

TABLE V

Number of Deaths during the Five-Year Period and Mean Annual Age Specific Death Rates per 100,000 Population from Acute Coronary Occlusion among White Persons in 20 Year Periods among Persons over 25 Years of Age in Philadelphia from January 1, 1933 to December 31, 1937, Based on Certain Countries of Birth (From U. S. Census of 1930)

Country of Birth	Total over 25 Yrs. of Age			25-44 Years of Age			45-64 Years of Age			65 Years and over		
	Population	Deaths	Mean Annual Rate per 100,000	Population	Deaths	Mean Annual Rate per 100,000	Population	Deaths	Mean Annual Rate per 100,000	Population	Deaths	Mean Annual Rate per 100,000
United States.....	650,478	2904	89	389,993	247	13	202,169	1428	141	58,316	1229	421
Russia.....	72,310	603	167	40,459	32	16	26,998	393	291	4,853	178	734
Germany.....	34,132	252	148	11,642	7	12	14,739	83	113	7,721	162	420
Ireland.....	48,091	271	113	16,546	6	7	22,994	123	107	8,551	142	332
Austria-Hungary.....	16,553	128	155	8,800	10	23	6,723	76	226	1,030	42	816
Italy.....	61,118	182	60	35,527	16	9	21,329	121	113	4,262	45	211
England, Scotland and Wales.....	32,089	197	123	12,234	7	11	14,339	73	102	5,516	117	424
Poland.....	28,358	82	58	17,264	6	7	9,745	53	109	1,349	23	341

45-64 year age period, in which the mean annual death rate was 291 per 100,000 persons of Russian birth and 226 per 100,000 persons of Austrian birth. Among native born white Americans it was only 141 per 100,000 persons and among persons born in Ireland, Germany, Poland, and Great Britain it was even less.

Ninety-seven per cent of the deaths from this cause among persons born in Russia were among Hebrews. Based on rather incomplete returns the mean annual death rate was 67 per 100,000 Jewish persons as compared with 53 per 100,000 non-Jewish white persons. It seems likely that the mortality from acute coronary occlusion is slightly higher among all Jewish persons than among Gentiles. It is doubtful, however, if it is much higher among native born Jews than among white Gentiles.

Occupations of Decedents. During 1935-36, the United States Public Health Service conducted a National Health Survey. In Philadelphia, 122,270 persons, or about 6 per cent of the population, were enumerated. This group may be assumed to be a roughly representative sample of the population of Philadelphia as to age, race, sex and economic status. This sample included 18,417 white males between 35-64 years of age.

By determining the number of persons in each broad occupational group in each 10-year age period, and applying this sample to the total white male population in this age period, it is possible to estimate the number of professional men, proprietors, managers and officials, clerks and salesmen, and workers of all classes including foremen in each 10-year period among the white male population between 35-64 years of age. This is the age period among gainfully employed persons in which deaths from this cause are most common. By applying the same occupational code to the occupations listed on death certificates it is possible to estimate the age specific mortality rates per 100,000 persons in each occupational group.

Based on this estimate, the mean annual mortality rate in the age period 35-64 years was 154 per 100,000 professional men, 140 per 100,000 proprietors, managers and officials, 128 per 100,000 clerks and salesmen and only 107 per 100,000 workers (table 6). In the 55-64 year age decade the estimated mean annual mortality rate was 475 per 100,000 professional men, 357 per 100,000 clerks and salesmen, 304 per 100,000 proprietors, managers and officials, and 253 per 100,000 workers.

Caution is suggested in interpreting too literally the high mortality rate from acute coronary occlusion among professional men. It is possible that higher standards of diagnosis prevailed among this occupational group. It is difficult to understand, however, why the standards of diagnosis should be higher among this group, with the exceptions of physicians, than among business men. This study should be repeated at the end of another five-year period when the diagnosis of this condition has had an opportunity to become better stabilized among all occupational and social classes. It is interesting to note that such estimates as are available at the present time

indicate a higher incidence of this disease among professional men and the lowest incidence among workers.

Is Acute Coronary Occlusion Increasing? During the quinquennium under study the number of deaths attributed to this cause increased 126 per cent. Is this increase genuine? To what extent is it fictitious? What factors, other than an actual increase, may be invoked to explain why more deaths were reported each year as due to this cause? Have general practitioners become sufficiently adept in the diagnosis of acute coronary occlusion to permit many definite conclusions?

TABLE VI

Estimated Number of White Males between 35-64 Years of Age in Each Occupational Group by 10-year Age Periods, Number of Deaths from Acute Occlusion among White Males between 35-64 Years of Age by 10-year Age Periods According to Occupation, and the Estimated Mean Annual Age Specific Mortality Rates per 100,000 Persons in Each Occupation Group in Philadelphia from January 1, 1933 to December 31, 1937.
Deaths Are Listed on a Five-Year Basis

Occupational Groups	35-44 Years			45-54 Years			55-64 Years			Total: 35-64 Years		
	Estimated Population	No. of Deaths	Estimated Mean Annual Death Rate	Estimated Population	No. of Deaths	Estimated Mean Annual Death Rate	Estimated Population	No. of Deaths	Estimated Mean Annual Death Rate	Estimated Population	No. of Deaths	Estimated Mean Annual Death Rate
Professional men....	7,684	18	47	5,145	28	109	3,284	78	475	16,113	124	154
Proprietors, managers, and officials..	18,462	34	37	17,144	129	150	10,463	159	304	46,069	322	140
Clerks and salesmen..	25,915	47	36	14,780	109	147	9,139	163	357	49,834	319	128
Workers—all classes..	81,641	118	29	59,677	371	124	36,083	456	253	177,401	945	107
Total.....	133,702	217	32	96,746	637	132	58,969	856	290	289,417	1710	118

These and many other questions present themselves. It is doubtful if any of them can be answered categorically at this time. It is well to take stock, even though it is not possible to make a complete inventory of all of the factors involved. In attempting to arrive at some conclusions, certain possible considerations will be reviewed for the purpose of elimination. Having disposed of them, the remaining factors will be considered in greater detail:

1. The increase in reported mortality is not due to an undue tendency to report deaths among persons past 70 years of age as due to this cause. The reported mortality compares quite closely to the age distribution of diagnoses confirmed at necropsy. The age distribution remained practically the same during these five years under study.

2. Conversely, the increase was not due to relatively more deaths occurring in age periods prior to 60 years.

3. Although the aging of the population was doubtless a factor, it was not sufficient to account for an increase of 126 per cent in five years. Deaths from all causes, and from such diseases as cancer, diabetes mellitus,

and all heart disease did not increase to that extent. Furthermore, acute coronary occlusion did not appear to be primarily a problem of the aged.

4. The increase cannot be attributed, to any appreciable extent, to the aging of the foreign born population, over and above the aging of the general population. Deaths attributed to this cause increased 141 per cent in the period under study among the native born population, but only 132 per cent among the foreign born population.

5. The increase could not be explained on the basis of changes of terminology in diagnosis. According to the records of the Philadelphia Health Department there were only 10 per cent fewer deaths attributed to angina pectoris in 1937 than in 1933, while deaths attributed to all forms of coronary disease increased nearly 100 per cent.

This leaves two important considerations: improvement in diagnosis and the possibility of an actual increase. Of these two factors, better diagnosis appears to be the most outstanding. While the clinical diagnosis of acute coronary occlusion was well recognized by internists and cardiologists by the beginning of the year 1933, the next five years were characterized by a better appreciation of the clinical diagnosis of this condition by the mass of practising physicians. Time is required for the leaven to work. There is always a lag between discovery and popular acceptance.

Furthermore, during these five years many advances were made in the diagnosis of this condition, notably in the use of precordial leads and better recognition of atypical cases. Contrariwise, there was also considerable improvement in the differentiation of acute coronary occlusion from other conditions. This tends to reduce the number of deaths attributed to this cause. With regard to improvements in electrocardiographic diagnosis, it should be borne in mind that most fatal cases are diagnosed on the basis of the clinical picture, and without the aid of this valuable diagnostic adjunct.

Granting that improvement in diagnosis is the major factor responsible for the increase in reported mortality, is it the only factor? Among regularly admitted patients to 26 civilian hospitals approved for internship by the American Medical Association, deaths attributed to acute coronary occlusion increased 70 per cent during these five years, while admissions for all causes increased 9.5 per cent. In a group of 11 selected hospitals, most of which are teaching institutions and whose staffs have been especially interested in this problem, the number of deaths attributed to this disease increased 60 per cent in 1937 over 1933. Can it be stated with justification that the diagnostic acumen of the staffs of these hospitals increased to that extent in so short a period? It is difficult to escape the impression that the increase in reported mortality from acute coronary occlusion may have been in part due to a certain actual increase in this disease.

It is doubtful if the increase in deaths from this cause can be attributed to any great extent to greater interest in this problem, as a result of which more patients were admitted to hospitals. Of the deaths attributed to acute

coronary occlusion in 1933, 17 per cent occurred in hospitals, while in 1937 only 12.8 per cent occurred among regularly admitted patients to hospitals approved for internship by the American Medical Association.

Furthermore, there was an increase of 135 per cent in the reported mortality from all sources among white persons as compared with only 22 per cent among colored persons during these five years. There was an increase of 78 per cent in the number of deaths, attributed to this cause among white persons in hospitals approved for internship by the American Medical Association, but no increase among Negroes. In hospitals especially both races were subjected to the same diagnostic standards. If improvement in diagnosis were the only factor, the *percentage increase* should have been approximately the same for the two races. Since this did not prevail, it seems likely that a part of this increase may actually have been due to more deaths from this disease among white persons.

SUMMARY

During the 5-year period between January 1, 1933 and December 31, 1937, there were 5116 deaths reported as due to acute coronary occlusion and other nearly synonymous diagnostic terms in Philadelphia. The age distribution of these deaths corresponded quite closely to that of cases in which the diagnoses were based on necropsy findings. Despite an increase of 126 per cent in the number of deaths reported as due to this cause during this period, the age distribution and mean ages at death were nearly the same in each of the five years under study.

Acute coronary occlusion is not primarily a problem of the aged. Only 24.5 per cent of deaths reported as due to this cause occurred among persons past 70 years of age. The peak incidence, 32.9 per cent, occurred in the 60-69 year age period. Of the total deaths attributed to this cause 41.9 per cent occurred among persons younger than 60 years of age. In the 50-59 year age period, acute coronary occlusion was the cause of 26.0 per cent of all deaths reported as due to heart disease. With each succeeding decade this condition accounts for a smaller percentage of the total heart disease mortality. Only 5.5 per cent of deaths from heart disease among persons past 80 years of age were attributed to acute coronary occlusion.

The mean age at death was 61.2 years. The mean ages and age distribution indicated deaths at younger ages among coroner's cases and somewhat older ages among deaths occurring in the homes. The mean ages at death among males was younger by more than four years than among females. Although the mortality rates indicated relatively fewer deaths among Negroes, the mean age at death among colored persons was younger by several years than among white persons.

The mean annual mortality rate was 53 per 100,000 white persons; 76 per 100,000 white males, but only 37 per 100,000 white females. The mean

annual mortality rate was 21 per 100,000 colored persons; 23 per 100,000 colored males and 19 per 100,000 females. The mortality rate among white persons increased from 36 per 100,000 in 1933 to 84 per 100,000 in 1937. Among Negroes it only increased from 25 per 100,000 in 1933 to 28 per 100,000 in 1937. In some of the intervening years it was even lower than these figures among Negroes.

The monthly incidence of deaths indicates considerably more deaths from this cause during the colder months than in the summer.

Based on estimated mortality rates, professional men appeared to be more likely to die from this cause than other occupational groups, especially workers. Since it is not known whether the diagnoses of acute coronary occlusion are made with equal accuracy among persons in various occupational groups at the present time, caution is suggested in interpreting the higher reported mortality among professional men too literally.

The increased reported mortality from acute coronary occlusion of 126 per cent in five years could not be accounted for to any great extent by more deaths among the aged reported as due to this cause, by an aging of the population in general or the foreign born population in particular, or by changes in diagnostic terminology. Improvement in diagnosis appeared to be the most important factor responsible for the increase in reported mortality. Doubt is expressed whether an increase of 70 per cent in deaths attributed to this cause in 26 civilian hospitals approved for internship by the American Medical Association or an increase of 60 per cent in 11 selected hospitals during these few years can be *entirely* explained on the basis of improvements in diagnosis.

Deaths reported as due to acute coronary occlusion among white persons regularly admitted to hospitals approved by the American Medical Association increased 78 per cent, while there was no increase in deaths from this cause among colored patients. Since both races are subjected to the same diagnostic standards, the *percentage increase* should have been about the same if better diagnoses were the only factor. The possibility of a certain degree of actual increase in mortality from acute coronary occlusion should not be dismissed summarily.

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OBSERVATIONS UPON THE EXPERIMENTAL AND CLINICAL USE OF SULFAPYRIDINE. III. THE MECHANISM OF RECOVERY FROM PNEUMOCOCCAL PNEUMONIA IN PATIENTS TREATED WITH SULFAPYRIDINE *

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It has been established by a number of investigators^{1, 2, 3, 4, 5} that sulfapyridine exercises a bacteriostatic effect upon pneumococci in vitro. Fleming¹ has shown that the growth of pneumococci in human whole blood is inhibited by sulfapyridine, but that in the absence of leukocytes the organisms are not destroyed. When leukocytes are present in the blood-sulfapyridine preparations, the growth of pneumococci is not only inhibited, but in many instances the blood is rendered sterile, probably as a result of the combined action of the sulfapyridine and the natural antibacterial substances in the serum. If type-specific pneumococcal antiserum is added to similar preparations, this sterilizing effect is greatly enhanced.

Likewise in vivo the action of sulfapyridine seems to be principally bacteriostatic. We⁶ have studied the effect of sulfapyridine therapy upon the evolution of experimental pneumococcal peritonitis in mice, and have noted that the drug inhibits the multiplication of pneumococci in the peritoneal cavity. However, very little phagocytosis has been noted in the peritoneal exudates, and unless therapy with sulfapyridine is maintained for several days, the organisms resume active multiplication as soon as treatment is discontinued. When, on the other hand, the mice are treated with a small amount of antipneumococcal serum during the phase of bacteriostasis, the pneumococci become opsonized and are quickly destroyed by phagocytosis.

These facts suggest that type-specific antibodies play an important rôle in the process of recovery from pneumococcal pneumonia following treatment with sulfapyridine. Since no study of the antibodies in the serum of patients ill with pneumococcal pneumonia and treated with sulfapyridine has been reported, it is thought advisable to present certain data bearing upon this point.

METHODS

The antibody content of the serum of 12 patients ill with lobar pneumonia caused by pneumococci of types I, II or III was followed during the course of sulfapyridine therapy. Specimens of blood serum were obtained

* Received for publication July 1, 1939.

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This investigation was supported by a grant from The Chemical Foundation, Inc., of New York City.

just prior to the start of treatment with sulfapyridine and then at two day intervals until the patients left the hospital. The antibody content of these specimens of serum was subsequently determined by mouse-protection tests. A pure bred strain of mice (C. F. 1) was used in all experiments. Each mouse was injected intraperitoneally with 0.5 c.c. of varying dilutions of a 14 hour rabbit's blood broth culture of pneumococci immediately after having received by the same route 0.5 c.c. of a 1 to 5 dilution of the serum to be tested. The culture dilutions varied logarithmically from 1:5 to 1:50,000,000. Five mice were injected with each dilution of culture. The pneumococci of types I, II and III used in these tests were cultured only after several mouse passages and were all highly virulent, 10^{-8} c.c. of a 14 hour culture killing control mice regularly in 20 hours. Each test was terminated after 96 hours, and all mice living at the end of this time were counted as survivals. The final results were calculated in terms of antibody units * per c.c. of the patient's serum.

RESULTS

The results of the antibody studies are summarized in table 1. The day of essential recovery is taken as that day upon which the rectal temperature became essentially normal (below 99° F.) and after which the patient's course in the hospital progressed uneventfully.

It will be noted that essential recovery from the pneumonia occurred in seven of the 12 cases before specific antibody could be detected in the serum. In chart 1 the graphic record of such a case is presented which shows that although essential recovery occurred on the fifth day of disease (and the third day of treatment) antibody could not be detected in the patient's serum until the seventh day. No antibody was found at any time in the serum of the one patient in the group who failed to recover. Also one patient who recovered promptly from type I pneumonia showed no antibody in the blood serum even 16 days after the onset of his illness. No later specimens of serum were examined.

COMMENT

The results of these studies in patients ill with pneumococcal pneumonia treated with sulfapyridine are in agreement with similar observations made by McIntosh and Whitby⁵ in experimental pneumococcal infections. They found that mice infected with pneumococci and treated with sulfapyridine developed a type specific immunity to the organism causing the infection. The time of appearance and titre of antibody in the serum of the treated animals was observed to be approximately the same as that found in the untreated mice immunized with doses of killed pneumococci calculated to be comparable to the immunizing dose of living cocci in the treated animals. Thus, it appeared that the immune response of the mice was in no way altered

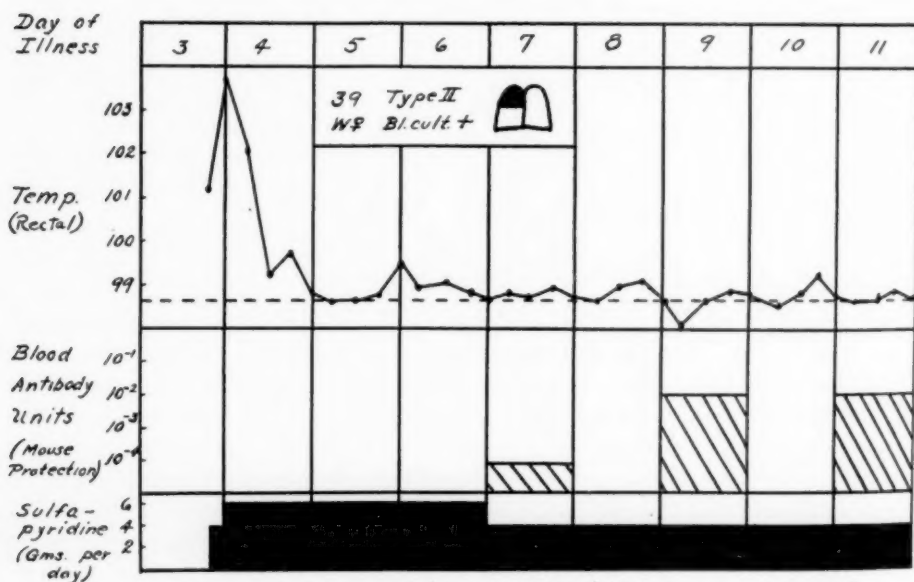
* 1 unit = The amount of antibody which protects against 1,000,000 lethal doses of pneumococcus.

TABLE I

The Appearance of Type Specific Pneumococcal Antibody in the Sera of Patients Ill with Lobar Pneumonia and Treated with Sulfapyridine

Pa- tient's Hosp. No.	Type of Pneu- mococ- cus	Time of Development and Titer of Antibodies (Day of Disease—units per c.c.)															
		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
160955	I			0	*	10^{-4}		10		10		10					
160947	"	0		0		10^{-4}		10^{-3}		10^{-1}							
160964	"			0			0	*	10		10						
161304	"					0	*	0		0		0		0		0	
165765	"		0	*		10^{-5}		10^{-3}									
162439	"		0	0			*		10^{-3}			10^{-1}					
164268	II		0	0			10^{-1}		10^{-1}		10^{-1}		10^{-1}		10^{+}		10^{+}
165533	"		0	*			10^{-4}		1		1		1				
165784	"			0	0		0			0	0	Died					
160992	III			0		0	*	0		10^{-1}		10^{-1}					
160993	"			0			*		0								
165521	"		0	*			0		0	10^{-4}		10^{-4}		10^{-4}			

* Day of essential recovery.



1 unit of antibody protects vs. 1,000,000 lethal doses of pneumococci.

CHART I. Blood antibodies (mouse protective) in pneumococcal pneumonia treated with sulfapyridine.

by sulfapyridine treatment. Likewise, it may be concluded from the present study that the antibody response of patients with pneumonia treated with sulfapyridine is much the same as that observed in untreated patients during the natural course of the disease.

The fact that antibodies may not appear in the serum until several days after fever has subsided suggests a possible explanation for the frequent relapses suffered by patients with pneumonia who have been treated sparingly with sulfapyridine. In their first series of patients treated with the drug, Evans and Gaisford⁷ observed on several occasions, secondary pyrexia following early withdrawal of therapy. In certain of these cases the secondary rise in temperature was associated with a spread of the pneumonia. Dreosti⁸ treated 100 patients with sulfapyridine, stopping the drug after two to four days of normal temperature; 10 per cent of them suffered relapses. Alsted⁹ has recently described six cases of type III pneumonia in which the initial response to treatment with sulfapyridine was satisfactory. Five relapses occurred among the six cases, four of the patients requiring additional therapy. In a previous publication we¹⁰ have reported two comparable cases of relapse due to inadequate treatment with sulfapyridine.

As already mentioned, sulfapyridine seems to act only as a bacteriostatic agent in pneumococcal infections. Its primary effect in pneumonia is probably to hold in check the pneumococcal infection in the lung. There is adequate experimental evidence favoring the view that the eventual destruction of pneumococci within the lung, and thus the final recovery from pneumococcal pneumonia, depends upon phagocytosis. Since encapsulated pneumococci are known to be resistant to phagocytosis unless opsonized by specific antibody, it is only logical to conclude that type specific antibodies play an important part in the process of final recovery. If, in any given case of pneumonia, a bacteriostatic agent such as sulfapyridine is withdrawn before sufficient antibodies have developed to promote phagocytosis,* a relapse of the pneumonia is likely to ensue. A normal temperature does not necessarily indicate complete recovery.

Relapses may be avoided by continuing sulfapyridine treatment over a sufficiently long period of time.¹⁰ If toxic reactions to the drug necessitate an early withdrawal of therapy, it would seem advisable to treat the patient with antipneumococcal serum unless immunological tests have revealed the presence of an excess of antibody in the blood. We have found the skin test with type-specific capsular polysaccharide,^{12, 13, 14} a valuable index of antibody in such cases. The skin test may also be used routinely as a guide to sulfapyridine therapy, for if it is performed at daily intervals, treatment may be safely discontinued in uncomplicated cases of pneumonia as soon as the test becomes positive. It should be pointed out, however, that a positive skin test is occasionally observed in certain cases complicated by pneumococ-

* It is possible that sufficient immune bodies may accumulate locally in the lung before an excess can be detected in the blood.¹¹ Thus an absence of circulating antibody does not necessarily indicate that a relapse must invariably occur if treatment is discontinued. (See fourth case in table I.)

cal empyema, meningitis, and endocarditis¹⁴ where further chemotherapy is usually indicated. By the use of the skin test with type-specific capsular polysaccharide it may be possible to shorten the required period of chemotherapy to a minimum, thus decreasing the chance of toxic reactions to the drug without subjecting the patient to the risk of suffering a relapse.

Finally it is a fact of considerable theoretical significance that under sulfapyridine treatment the fever may be controlled several days before antibodies are detected in the blood. In the average untreated case of pneumococcal pneumonia antibodies appear in the serum at approximately the time of natural crisis.^{15, 16, 17} Therefore, it cannot be maintained that the abrupt fall in temperature usually effected by adequate sulfapyridine therapy is due necessarily to a coincidental natural crisis. The drop in temperature must in the majority of cases be attributed to the direct action of the drug.

SUMMARY

1. Type-specific antibodies often do not appear in the blood serum of patients ill with pneumococcal pneumonia and treated with sulfapyridine until several days after the temperature has fallen to normal.
2. Evidence is presented that type-specific antibodies play an important rôle in the process of recovery from pneumococcal pneumonia following treatment with sulfapyridine.
3. The lateness of the appearance of circulating antibodies is offered as a possible explanation for the relapses which frequently occur when sulfapyridine therapy is discontinued too soon.

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OBSERVATIONS ON TOXICITY AND CLINICAL VALUE OF STROPHANTHIN*

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THE efficacy of strophanthin in cardiac failure was studied carefully in a large series of patients by Fraenkel⁷ in 1906 and by Vaquez²⁸ in 1909. Their enthusiastic reports stimulated great interest in the therapeutic possibilities of this drug with the result that numerous observers soon corroborated their favorable results. The scope of this report is too limited to permit a complete survey of the very extensive literature on this subject, but the excellent monograph of Fraenkel⁸ will be found to contain a critical digest of practically all work done on the pharmacological and clinical aspects of strophanthin. It can be stated, however, that the available literature is almost exclusively favorable so that the use of strophanthin has now become an established procedure in Europe, particularly in France and Germany. The widespread acceptance of this drug abroad is in striking contrast to the reluctance which physicians in this country still display to the use of strophanthin in cardiac failure. Such hesitancy is based chiefly on the opinion that strophanthin is dangerous, that it can be given only by intravenous injection and that digitalis given orally can produce all the beneficial effects claimed for strophanthin without the attendant dangers. This striking divergence of opinion prompted us to re-investigate the problem, particularly with reference to toxicity, electrocardiographic changes and clinical effects in normal persons and in patients with cardiac failure in order to compare our results with those of foreign observers.

It is generally accepted that the pharmacological properties of strophanthin and digitalis are practically identical except that the former acts more promptly and is eliminated with greater speed (Fraenkel,^{8,9} Lendle,^{17,18} Wallace and Van Dyke,²⁴ Weese²⁵). The faster elimination or destruction of strophanthin is an important factor in reducing its cumulative action and toxicity after repeated injections. The clinical and electrocardiographic manifestations of strophanthin toxicity are also the same as those of digitalis, although Aschenbrenner¹ states that therapeutic doses of strophanthin are less likely to produce changes in the ST segment of the electrocardiogram than comparable doses of digitalis. Such comparisons should not, however, tempt the physician to use strophanthin in doses larger than those in the therapeutic range. Gold, Hitzig, Gelfand, and Glassman¹¹ found that a given toxic dose of digitalis did not always produce constant effects, even in the same patient. They also observed that a better response

* Received for publication October 31, 1938.

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Aided by a grant from the A. B. Kuppenheimer Fund.

could sometimes be obtained from the same dose after a suitable rest period. We have observed similar variations in response and have noted frequently that patients will react better to digitalis after edema or effusions are removed. Eckey⁶ reports patients who are hypersensitive to strophanthin since they showed toxic effects after 0.3 mg. of strophanthin given daily for two days. Caution is advised by Dieckhoff and Schulze⁴ in diphtheria because they found the cat's heart to be hypersensitive to digitalis and strophanthin if previously injured with diphtheria toxin. A number of suggestions have been offered by which toxic effects of strophanthin might be decreased. Bischoff^{2,8} suggested the addition of 0.1 or 0.2 gm. of caffeine sodium benzoate to the strophanthin in order to reduce the toxicity of the latter. The method has not been accepted generally and its value is questioned by several observers. Rothberger and Zwillinger²¹ observed that magnesium sulphate could restore normal rhythm in animals poisoned by strophanthin provided ventricular fibrillation was not present. Zwillinger^{29,30} found magnesium sulphate effective in man when given intravenously for extra-systoles and heart block caused by strophanthin. Fraenkel⁸ and others have found strophanthin K somewhat less toxic than ouabain, and about 30 per cent less toxic than strophanthin G. This greater safety and the fact that strophanthin K is more soluble in water than the other preparations are the chief reasons for preferring this preparation, although the others also produce excellent results.

Extensive experience by a number of observers over many years has shown that strophanthin is no more dangerous than digitalis if used in proper dosage and in suitable patients. Practically all untoward results in the past were due to dosage which was far too great or administration of strophanthin in patients who had received large doses of digitalis or who showed definite evidence of previous digitalization. Grünbaum¹² has given over 10,000 injections of strophanthin during the past 10 years without observing a single death directly attributable to the drug and Fraenkel with a larger experience is equally convinced of the safety of strophanthin if given in the proper manner. It is well to remember that the average maximum initial daily dose, 0.5 mg. of strophanthin, is equal to the effect of approximately 300 mg., or less than 5 grains, of digitalis. Such a dose of strophanthin is usually sufficient for the first 24 hours, but the total digitalis equivalent is still low even if an additional smaller dose of strophanthin is required in very severe cases. It should be mentioned in passing that failure was encountered in patients in whom neither strophanthin nor other cardiac remedies were indicated, such as in tachycardia of thyrotoxicosis, various arrhythmias, heart lesions not associated with cardiac failure, acute infectious myocarditis and in moribund patients.

The fact that strophanthin can be administered only by intravenous injection should not preclude its use in patients where the intravenous route is preferable to oral administration or when the former method is the only one practicable. Weese²⁵ pointed out that intravenous injection of stro-

phanthin permitted rapid administration of an exact dose capable of an early and intense effect. There is thus no necessity for doses approaching toxic limits when rapid effectiveness is desirable and where cumulative action is undesirable. Intravenous administration is also of value in the presence of congestion of the liver or of the gastrointestinal tract where absorption of oral medication may be greatly delayed. Fraenkel and Thauer¹⁰ observed that hepatic congestion interfered with the efficacy of digitalis administered orally and believed the cause to be stagnation of large amounts of blood in the liver with the result that a greater part of the orally ingested digitalis is retained by that organ leaving less for transport to and fixation by the heart. It is no simple matter to estimate the exact dose of digitalis necessary for a full effect when given orally. Weese does not believe that one can compute the required dose for full digitalization by using the weight of the patient as a guide. He believes that other factors are operative, such as the reserve still inherent in the heart, the degree and type of heart failure, its underlying cause, and the uncertainty of absorption from the gastrointestinal tract in the presence of passive congestion. To these may be added the presence or absence of auricular fibrillation, the weight of retained water in edema, and the amount of excess fat in obese patients.

Weese²⁶ showed that slow intravenous injection exposes the heart for a longer period to the strophanthin contained in the blood with the result that a greater proportion of the given total dose is taken up by the heart. This is the reason for advocating very slow administration, even diluting the preparation with 10 to 20 c.c. of 10 per cent dextrose solution. This author^{26, 25, 27} and Lendle¹⁶ found that about 9 per cent of the minimum lethal dose of strophanthin is fixed to the heart after intravenous injection, the remainder being taken up by the skeletal muscles, liver and kidneys. The lungs and blood do not take up appreciable quantities of the drug, a point of importance in calculating dosage by intravenous injections. Weese also showed that as much as an entire minimum lethal dose is absorbed by the heart and other tissues in one circulatory cycle, thus showing the rapidity with which strophanthin is absorbed after intravenous injection. The real advantages of strophanthin are, however, rapidity of absorption and of effect, exactness of dosage, a fairly accurate idea of how much of an injected dose will be fixed to the heart, and the avoidance of uncertainty in absorption in the presence of venous stasis in the liver or gastrointestinal tract (Herzog¹⁴ and Fraenkel⁸). These advantages, rather than properties not possessed by digitalis form the basis for the choice of strophanthin in certain instances of cardiac failure.

The many reports of excellent clinical results with strophanthin are particularly impressive when it is remembered that many of the patients suffered from cardiac failure with regular rhythm; the underlying basis being coronary sclerosis or hypertension. Vaquez,²³ Fraenkel,⁸ Edens,⁵ Zak,²⁸ Zimmermann-Meinzingen and Jagic¹⁵ reported success with intravenous injection of strophanthin in patients who failed to respond to digi-

talis administered orally. Fraenkel recommends strophanthin in cardiac failure of any variety and points out that it is the failure and not its cause which requires the drug. Strophanthin is stated to be very effective in comparison with digitalis in acute cardiac emergencies such as cardiac asthma or abrupt congestive failure of mitral disease where the dosage must be exact and where absorption from the congested gastrointestinal tract is uncertain. Oral digitalis even in very large doses does not act for about two hours, an interval obviously too long in such cardiac emergencies. Fraenkel states that cardiac failure in hypertension is one of the special fields where strophanthin shows its superiority over digitalis. This is of importance since it is well known that digitalis orally may fail in such patients.

METHOD AND RESULTS

We decided to use the utmost caution in our experiments and at first disregarded statements in the literature that strophanthin was safe when used in the manner previously described. We took advantage of the well known pharmacological fact that strophanthin and digitalis in therapeutic doses produce practically no manifestations in normal persons. A solution of strophanthin K was used, 1 c.c. of which corresponded to 0.25 mg. of strophanthin activity according to U. S. P. XI specifications.* The preparation was put up in hard glass rubber-stoppered bottles and no appreciable deterioration could be ascertained one year after being placed in such containers in accordance with the suggestions of R. L. Levy and G. E. Cullen.¹⁹ The intravenous injections were given slowly, no less than 20 seconds being consumed with an undiluted solution and a longer period when diluted in dextrose solution. All patients were observed for nausea, vomiting, precordial oppression, arrhythmia and other signs of toxicity. Electrocardiograms were made before injections and at varying intervals after administration.

The first group to be studied consisted of nine normal persons without history or evidence of cardiac disease. All were kept in bed and a control electrocardiogram consisting of the three standard leads was made before administration of the drug. Strophanthin 0.5 mg. was then injected intravenously and electrocardiograms were made at intervals of five, 15, 30, 60 minutes, two hours and 24 hours after injection. We disregarded minimal changes in amplitude, that is, of 1 mm. or less, because one of us had observed previously that such slight changes can occur without apparent cause. None of these patients showed clinical evidence of toxicity. The electrocardiogram after injection showed moderate slowing of the heart rate in three instances, beginning in five minutes and disappearing after two hours. The T-wave became inverted only once, the change being seen only in Lead III. These results convinced us that 0.5 mg. was a safe dose and

* The Abbott Laboratories furnished us with the supply of strophanthin K and at our request assayed its potency from time to time.

prompted us to study the effects of 0.75 mg. in four normal persons in a similar manner. No clinical or electrocardiographic evidence of toxicity was observed after this dose, an amount distinctly above the ordinary maximum used during the first 24 hours.

We then studied the effects of continuous use of strophanthin in 13 patients with cardiac failure, 11 of whom had hypertensive cardiac insufficiency with regular rhythm, and two with failure from old rheumatic heart disease with auricular fibrillation. All patients were severely decompensated as evidenced by marked dyspnea and orthopnea, extensive edema, marked congestion of the lungs and liver, and engorged cervical veins. A control period of from three to five days was maintained during which the patients were kept at absolute bed rest except for daily weighing. Control electrocardiograms were taken in the usual manner, including precordial leads, the total fluid intake was limited to 1200 c.c. daily, the urine output for 24 hours was measured, and a soft diet without salt restriction was used in all instances. Placeboes were given to all patients during this period and small doses of morphine or barbiturates were used only when absolutely necessary. No drugs acting directly on the cardiovascular system were employed during this time. Daily observations were made of the pulse rate, body weight, urine output, degree of dyspnea, nocturnal dyspnea and orthopnea, extent of edema, evidences of pulmonary and hepatic congestion, degree of sweating and other subjective symptoms. Similar observations were made after strophanthin therapy was instituted, the electrocardiograms being taken daily 20 minutes after each injection. The initial daily dose of strophanthin was usually 0.5 mg. either as a single dose or as two injections of 0.25 mg. given at an interval of 12 hours. Occasionally only one dose of 0.3 mg. was given during the first day. Subsequent treatment consisted of daily injections of 0.3 mg. together with accessory medication when necessary. Such accessory treatment consisted of small doses of morphine at night in three instances and a mercurial diuretic in four patients.

There was marked clinical improvement in every instance. Many of the patients volunteered the information that they could breathe easier and felt definitely better shortly after the first injection of strophanthin. Some of the patients actually went to sleep about one hour after the drug was administered. The majority could sleep without the aid of hypnotics or sedatives and paroxysmal nocturnal dyspnea no longer occurred. We have already mentioned that sweating became greatly increased in some instances after strophanthin, the patients stating that their bedclothes were actually drenched during the night. We also observed at times that the loss in body weight was sometimes marked when the urinary output was not greatly increased, a change attributed to increased extrarenal water loss. Daily electrocardiograms showed no significant changes except one instance in which transient prolongation of the PR interval from 0.16 to 0.22 second occurred. This change disappeared during the next day in spite of the fact that the same dosage of strophanthin was maintained. The T-wave in

Lead III or IV became changed in direction as compared with the control in three instances, but no further electrocardiographic changes were noted in spite of continued use of strophanthin in the same dosage. None of the patients presented clinical evidence of strophanthin toxicity. Four of the patients with severe hypertensive failure who had been on previous management with digitalis therapy with moderate or no benefit showed a striking response to strophanthin.

The following case reports will illustrate the course of some of these patients:

CASE REPORTS

Case 1. E. W., male, aged 63, colored, entered the Michael Reese Hospital on February 17, 1938. Dyspnea had been present for the past two years and was becoming rapidly worse. Dull substernal pain and pain in the left shoulder were present. His dyspnea was practically constant. There had been marked progressive edema of the ankles especially in the preceding four days. Cough with blood-tinged sputum had been present for some time and headache and vertigo had become prominent during the past few weeks. He had had typhoid fever in 1907, "rheumatism" as a child, and gonorrhea and chancre 25 years previously with practically no treatment. The essential findings on examination were: Extreme dyspnea and orthopnea, engorged pulsating cervical veins, inspiratory and expiratory wheezing and sonorous râles diffusely and crepitant râles in both bases of the lungs posteriorly. The apex beat was palpable in the sixth interspace, to the left of the midclavicular line. The heart tones were distant and an occasional extra-systole was heard. The abdomen was tense and distended, the liver edge being palpable six fingers-breadth below the costal margin. Shifting dullness in the flanks and a fluid wave could be elicited. The scrotum was markedly edematous and extensive edema was present in both lower extremities. The blood pressure was 240 mm. of mercury systolic and 130 diastolic. A teleoroentgenogram showed enlargement of the right auricle and left ventricle with a cardiothoracic ratio of 18-31. Fluid was seen at both bases and the hilus markings were denser than normal. The blood chemical and serological tests were normal. The patient was observed for eight days under control conditions, being at absolute bed rest and receiving small doses of luminal and ephedrin in addition to the experimental measures previously mentioned. Morphine sulphate $\frac{1}{4}$ gr. subcutaneously was administered for extreme restlessness once during this period. His weight during the control period varied from 151 to 154 lbs.; his total fluid intake in 24 hours ranged between 36 and 48 oz., and his urine output between 37 and 47 oz. per day. Strophanthin 0.5 mg. intravenously was then administered. Shortly after the administration of strophanthin the patient remarked that he had not felt so well in a long time and went to sleep. No further sedation was necessary and he slept well every night without the use of sedatives. Perspiration was perceptibly increased; dyspnea and wheezing were definitely reduced; the weight steadily diminished to 135 lbs. 12 days after the first injection of strophanthin, although the intake and urinary output remained unchanged. He received 0.3 mg. of strophanthin daily after the first injection until his discharge, at which time he felt very much improved. He was instructed to take maintenance doses of digitalis while at home in order to hold the improvement acquired during his hospital stay. The only electrocardiographic change observed was a reversal of the T-wave in Lead IV, but no further change occurred on continued use of strophanthin.

Case 2. H. M., male, aged 56, entered the Michael Reese Hospital on March 26, 1938. He had been treated in the cardiac clinic with digitalis for four years. His symptoms began in 1934 with congestive failure for which he was hospitalized for

one week. There had been increasing dyspnea on exertion since that time and paroxysmal nocturnal dyspnea became more frequent. Edema of the legs was progressive and reached a marked degree at the time of admission. There was nothing of importance in the past history. Examination revealed an obese individual with orthopnea, engorged cervical veins and enlargement of cardiac dullness to the left and right. The apex beat was palpable in the left anterior axillary line, the heart tones were distant and regular, and a soft systolic murmur was present at the apex. The abdomen was difficult to palpate because of obesity but the liver region was distinctly tender. There was marked pitting edema of the lower extremities. The blood pressure was 190 systolic and 120 diastolic. A teleoroentgenogram of the heart showed the apex to be in the axillary line with a cardiothoracic ratio of 20-29.5 and marked passive congestion of the lungs was obvious. The specific gravity of the urine was 1.012 with an excessive amount of albumin on entrance but only a trace four days after treatment. The red blood count and hemoglobin were normal, the white count was 12,000 and the Wassermann and Kahn reactions of the blood negative. The patient was observed in the usual manner for a control period of four days during which time he received morphine sulphate $\frac{1}{4}$ gr. on two occasions for severe nocturnal dyspnea and phenobarbital gr. $1\frac{1}{2}$ daily. His weight during this control period varied between 230 and 236 lbs.; his total daily fluid intake varied between 18 and 34 ounces, and his urine output between 10 and 34 ounces. He showed no evidence of improvement during this control period. Strophanthin 0.5 mg. was injected once on the first and again on the second day, and 0.3 mg. were given daily thereafter. The patient stated that his precordial pain was less severe after the strophanthin was given and that he breathed with more comfort. Morphine for nocturnal dyspnea was required only once in the ensuing 20 days. No apparent increase in perspiration could be observed. It was of interest to note that the weight of the patient did not decrease during the first five days of strophanthin therapy and that his urine output was only slightly increased. This was in contrast to the striking subjective improvement. Ammonium chloride gr. 90 per day was given three days after strophanthin therapy was begun and continued throughout. Mercupurin 1 c.c. was injected intravenously on the fifth day of treatment but resulted in no appreciable change in weight or urine output. The weight began to decrease, however, on the third day after mercupurin, at which time the patient lost two lbs. Mercupurin was not repeated for an interval of 18 days but the patient's weight dropped gradually until it fell to 203 lbs. and his urine output rose. The electrocardiogram showed prolongation of the PR from 0.16 second to 0.22 second for one day but returned to normal, although strophanthin was continued as before.

DISCUSSION

A critical survey of the literature and the results of our own studies lead us to conclude that there is a definite place for strophanthin in the treatment of certain types of cardiac failure. Digitalis, orally, is unquestionably the most reliable drug in routine treatment but advantage must sometimes be taken of the quicker action and faster elimination of strophanthin, whose pharmacological properties are identical with those of digitalis. Strophanthin is thus an ideal drug in acute cardiac emergencies such as paroxysmal dyspnea, cardiac asthma, acute pulmonary edema of cardiac origin or abrupt congestive failure. The drug can be used in passive congestion of the liver and gastrointestinal tract due to heart failure when absorption of digitalis is uncertain if administered orally. Excellent results

can be obtained in cardiac failure with regular rhythm when associated with hypertension, and in the occasional case of failure where digitalis has proved unsatisfactory. Intravenous administration under such circumstances is certainly no real drawback nor is strophanthin dangerous if the proper precautions and dosage are used.

Strophanthin, whose action becomes apparent in a few minutes, must not be given to a patient who shows evidence of previous digitalization or who has been on digitalis for some time, since rapid additive effects may occur resulting in toxic manifestations. Weese²⁵ and Fraenkel⁸ believe that patients who have received moderate doses of digitalis may receive 0.15 to 0.2 mg. without danger, provided there are no evidences of marked digitalization such as arrhythmia, conduction disturbances, changes in the ST or T or the usual clinical signs of digitalis excess. The dose of strophanthin may then be slowly increased on subsequent days. It is wise to allow an interval of about five days to elapse before strophanthin is injected in a patient who has been previously well digitalized but there is no danger in administering maintenance doses of digitalis orally after the last dose of strophanthin has been used. The presence of extrasystoles in heart failure is not necessarily a contraindication to strophanthin as the arrhythmia may, at times, disappear when the myocardial circulation is improved. It is advisable, however, to be cautious in such instances by beginning with doses of 0.2 or 0.25 mg. instead of the usual 0.5 mg. We have noted disappearance of incomplete heart block and of inversion of the T-wave in Lead III or IV upon continued daily administration of strophanthin. Strophanthin will not eradicate arrhythmia or tachycardia, nor will this drug be of any value in hypertension or organic heart disease if cardiac failure is absent, nor can one expect strophanthin to produce miracles in moribund patients.

Most authors with large experience in the use of this drug suggest 0.3 mg. intravenously as an initial dose once in 24 hours for patients in moderate failure and 0.5 mg. when failure is severe. Subsequent injections of 0.3 mg. daily will usually suffice to maintain the effects of the drug for as long a period as necessary. Beneficial effects are apparent within a few minutes, particularly if the strophanthin is diluted in 10 to 20 c.c. of 10 per cent dextrose solution in order to provide for slow injection so that the heart can absorb a greater part of the total injected dose. Smaller doses at more frequent intervals have been recommended by Tiemann²² but Meyer²⁰ and others find this method inferior to the one previously described, even if the total dose per day was the same in both procedures.

No toxic effects, either clinically or electrocardiographically, were observed by us after single doses of 0.5 or 0.75 mg. intravenously in normal persons, nor were untoward results observed in patients with severe cardiac failure. Continued daily injections of 0.3 mg. for as long as 24 consecutive days failed to produce significant clinical or electrocardiographic evidence of toxicity. These results lead us to agree with Fraenkel and others that strophanthin is a safe remedy when used in proper dosage and in suitable

patients. The therapeutic effects observed by us were in every way comparable to those seen after adequate digitalization.

The rapid response, often in a few minutes after injection of an ordinary therapeutic dose, is a real advantage. Some of our patients would state voluntarily that breathing was easier shortly after receiving strophanthin and others would drop off to sleep. One could hardly expect such improvement for several hours even if large doses of digitalis were given. A further advantage was the absence of cumulative action after prolonged use and is in accordance with the view of Fraenkel⁸ that the daily maintenance dose of 0.3 mg. is eliminated or destroyed in 24 hours. We noted that several of our patients developed marked perspiration after strophanthin and lost considerable weight even when there was no appreciable increase in urinary output. Edema and evidences of passive congestion receded indicating that water loss cannot be estimated accurately by measurement of urinary output alone and that weighing of the patient is a much better index when this procedure is practicable. Fraenkel⁸ and Heineke¹³ arrived at similar conclusions and stated that extrarenal water loss may sometimes exceed the urinary output.

Accessory measures such as sedation and diuretics are sometimes necessary with strophanthin just as they are with digitalis. It is well known that diuresis is greatly enhanced in cardiac failure if the patient is digitalized for a few days before administration of a mercurial diuretic. No such preliminary treatment is necessary with strophanthin since this drug will have become effective before the mercurial diuretic begins to act. We do not mean, of course, that ammonium chloride or similar substances are unnecessary in those patients in whom the diuretic alone fails to act. We merely point out that strophanthin and the diuretic can be placed in the same syringe and be injected as one dose in those patients who do not require preliminary treatment with ammonium salts. Finally, our studies showed that strophanthin can be used in ambulatory patients and that maintenance doses of digitalis may eventually be substituted or the injections of strophanthin can be given at increasing intervals depending on the condition of the patient.

SUMMARY

1. Single intravenous injections of 0.5 or 0.75 mg. of strophanthin K in normal persons failed to produce significant clinical or electrocardiographic evidence of toxicity.
2. Similar absence of toxicity was noted after 0.3 or 0.5 mg. in patients with severe cardiac failure, the majority of whom also had hypertension and regular rhythm.
3. Continued injection of 0.3 mg. daily for as long as 24 days consecutively also failed to produce clinical or electrocardiographic evidence of toxicity in patients with cardiac failure.

4. Accessory measures such as sedation or diuretics were sometimes necessary as with digitalis.

5. The therapeutic results with strophanthin seemed comparable in every way to those obtained by adequate digitalization when digitalis is given orally.

6. We do not advocate strophanthin instead of digitalis in the routine management of cardiac failure. It is our impression, however, that strophanthin is a safe and rapidly acting drug when used in proper dosage and in suitable patients. Its properties are practically those of digitalis but its speed of action and safety render it an ideal drug in acute cardiac emergencies, in marked congestive failure where oral digitalis is absorbed with some uncertainty and in those instances where one wishes to try another drug when digitalis fails.

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THE CHOICE OF OVARIAN OR PITUITARY THERAPY FOR MENSTRUAL DISTURBANCES *

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DISTURBANCES in menstrual rhythm or in fertility are far more frequently due to hypofunction than to an increased rate of ovarian hormone production. Regularly recurring cycles of increasing and decreasing intensity of secretion are characteristic of the hormones of the ovary. In this cyclic character of its hormone production the ovary is unique among the glands, unless it be the anterior pituitary in its gonadotropic secretion. The adjustment of the ovarian cycle is influenced by so many and diverse factors that disturbances in its rhythm are not surprising. Such impinging factors include the activity of other organs, nutrient and endocrine materials, and possibly nervous system controls, as well as the indirect effects of deviations in health of other parts of the body. In its ovarian aspects, menstrual rhythm may be disturbed by alterations either in the duration or the intensity of follicular or luteal secretory activity. The duration as well as the intensity of the action of these hormones on uterus, breast, vagina and the brain will determine the character of the responses.

Failure of the ovarian cycle to be completed seems to be due to the failure of ovulation. This is far more common than was supposed a decade ago.¹ The occurrence of incomplete cycles may not preclude regularity in menstruation or occasional fertility in a given woman. Repeated failure of ovulation, however, is an obvious cause for sterility. So far as is known a corpus luteum is never formed in the human ovary unless ovulation has preceded.

There are thus three types of ovarian hormone disturbance: altered intensity of secretion of either of the hormones, altered duration of secretion, or incomplete cycles in which only the estrogenic hormone is produced.

If there were an increased intensity of estrogenic hormone production, the evidence should be found in the character of the endometrium, the vaginal epithelium, the mammary duct system, or the concentrations of hormone in blood or urine. The endometrial changes suggesting hyperestrinism are hyperplasia of the glands and excessive flowing.² But these results are also produced by long continued and essentially uninterrupted effect of estrogenic hormone, even in small amounts.³ Therefore endometrial hyperplasia cannot be accepted as evidence of hyperestrinism. From the study of vaginal smears, numerous cases of reduced stimulation are found, but excessive estrogenic effects have been seen only as a result of therapeutically administered estrogens. This method of diagnosis⁴ would be one of the

* Read at the New Orleans meeting of the American College of Physicians March 27, 1939.

best to demonstrate an altered intensity of hormone production, but to date no such cases have been reported. The mammary duct system has not yet been studied in human cases in sufficient numbers to allow its use as evidence on the point in question. Assays of blood and urine have been the chief sources of data for the diagnosis of quantitative variations in estrin secretion.⁵ But these diagnoses are open to serious criticism on two grounds: First, the assays do not distinguish between the three or more estrogens and their ester forms; second and more important is the fact that no assay method has yet been applied to a sufficient number of normally cycling and fertile women to define with certainty the normal standard of blood or urine content of these hormones. There can be no logical diagnosis of hyper- or hypofunction until the normal is defined. The problem is essentially the same as in interpreting basal metabolism, blood sugar concentration, or serum calcium level. Furthermore, difficulties are encountered because so much estrogenic hormone is destroyed by the liver⁶ that less than 10 per cent of injected estrin is recovered in the urine.⁷ Also, the excreted forms have a different biological activity than the original form secreted by the ovary,⁸ and quantitative recovery of estrogenic material from blood is difficult at best.

These details are cited in order to demonstrate the danger of accepting diagnoses of altered intensity of function based on any of the current methods. The vaginal epithelial studies of Papanicolaou and Shorr⁴ afford the nearest approach to quantitative assay, since the organism that produces the hormone also does the titrating, and only the end point has to be read. Even here the nutritional status of the woman may interfere, as in vitamin A deficiency. With the methods in use we can make diagnoses of hypofunction, based on tissue study (endometrium,⁹ breast, vaginal epithelium), and of distorted rhythm. Aside from the gynecological problems presented by occasional neoplasms, these syndromes can be described in terms of undersecretion or of shortened or prolonged secretion. No definite hypersecretion has been demonstrated. In connection with the secretion of the corpus luteum, chemical methods for estimating pregnandiol glycuronide¹⁰ have provided a quantitative measure of luteal function. There is little evidence of cases of excessive luteal activity, or of unusually prolonged secretion of progesterone excepting in pregnancy.¹¹

The case is quite different in anterior pituitary secretion of the gonadotropic factor. Animal work demonstrates a variable gonadotropic potency of the pituitary gland at different stages in the life cycle.¹² In the senile or the castrate animal there is increased content of the hormone. This has been substantiated in a few human glands, but most of the information about the human comes from urinary assays.¹³ These cannot be held to measure the productivity of the intact human gland in any exact way. All the evidence points to one conclusion: the production and excretion of gonadotropic material by the pituitary is increased markedly whenever the ovaries are inactivated, removed, or atrophy spontaneously. Study of the urine by

methods recently described¹³ will justify differentiation of hyperfunction of the pituitary from other causes of disturbance in menstrual cycles. The methods will not yet allow of such certainty in discriminations between normal and reduced pituitary activity. Currently when there is subnormal ovarian action, without other recognized cause, hypopituitarism is being assumed. This undoubtedly includes many cases where other factors interfere with completely normal cycles of follicle and corpus luteum secretion. But clinical reasoning, based on analogies, accessory data, and results of therapy, makes it certain that some cases of ovarian hypofunction are secondary to pituitary hypofunction.¹⁴ Similarly, disturbed ovarian rhythm is in some cases due to disturbed timing or rate of secretion of the gonadotropic factors without which there is no ovarian activity. Consequently we may classify cases of ovarian hypofunction or atypical rhythm with regard to pituitary gonadotropic activity: as characterized by normal, increased or decreased function. At present the methods for substantiating the pituitary part of the diagnosis are elaborate enough to be limited to investigative clinics.

It is to be hoped that ultimately it will be possible to differentiate those cases with ovarian hypofunction secondary to primary pituitary failure from the cases with decreased ovarian function followed by increased pituitary activity. The latter cases will be expected *a priori* to be poorly adapted to therapy with pituitary gonadotropic materials. They seem to represent what can most simply be described as premature climacteric. This is based on the assumption that the climacteric is due to the failure of the ovaries from some cause other than pituitary failure.¹⁵ The assumption appears increasingly justified, although the possibility of nutritional deficits as causes for disturbance of the mechanism are not taken into account.

With such a state of partial diagnostic certainty the clinician is called upon to treat a variety of disorders of menstrual regularity and of sterility. Omitting those in whom there is reason to believe that anatomic anomalies, neoplasms, infectious processes, poor hygiene, or male responsibility (sterility) are the chief concerns, we return to the dictum: the symptoms and findings, if endocrine, are probably due to deficient amount of secretion or to prolongation of the follicular secretion phase. This generalization holds true from menarche to menopause, although for varying reasons. There is no way by which to explain the occurrence of menorrhagia in one case, oligomenorrhea in another, amenorrhea in a third, variations in cycle length in a fourth, variations in amount of flow at different times in a fifth woman. In fact it is most common to find all these features occurring at one time or another in the same patient, demonstrating that these are relatively incidental features of the underlying cause: ovarian underactivity.¹⁴

The first inclination of the clinician some years ago was to use substitution therapy with estrogenic substances, to augment the supply which was then thought and is now known to be inadequate for normal menstrual cycles. This therapy will often relieve the subjective complaints of the

autonomic and mental type which are characteristic of the climacteric. Similar symptoms occurring early in the reproductive period¹⁶ do not prove the imminence of the climacteric, for they may continue through many years. Their relief, while gratefully received by the patient, must not be taken as evidence of cure. We know that ovarian secretions do not stimulate the ovaries. Hypofunction is therefore not helped by ovarian hormone substitution therapy. There may be temporary improvement in menstrual rhythm, sometimes reduction in menorrhagia, but there is seldom evidence of improved fertility from such treatment. This is obviously the most important test of its adequacy.

A disadvantage of ovarian substitution therapy is the inhibiting effect of the estrogenic hormone¹⁷ on the pituitary production of the gonadotropic hormone. Estrin is therefore held to be contraindicated if continued pituitary function and ovarian rhythm with fertility are the clinical goals. At least in animals it is possible by the use of large doses of estrin to interrupt cyclic action, disturb fertility, and therefore to simulate some of the clinical syndromes described. There is a little evidence that with the use of large doses of estrin given at appropriate times, and for brief periods, the pituitary secretions may be made to induce ovulation.¹⁸ Unfortunately the problem of inhibition of the pituitary by the estrogenic hormone, and the question of initiating ovulation by stimulating the pituitary with estrogen, both require quantitative study of a type which has heretofore been all but impossible. Methods are becoming available to make such theories susceptible of test.

Until more definite information is available concerning the effects of clinical doses of estrogens on the pituitary, and therefore indirectly on the ovaries, it is the part of wisdom to limit the use of estrogenic hormone preparations to those cases which can be classed as menopausal. If patient and physician agree that there is no need to strive for regular cycles, to maintain or restore fertility, or to be concerned about anything save subjective relief from distress, then the simplest course is to use sufficient doses of estrin to accomplish this relief.¹⁹ The route of administration may be by injection of aqueous or oil solutions, by vaginal suppositories, or by oral administration. The aqueous extracts are of low potency, and seldom used. Oil solutions are available in a variety of potencies. Until the ultimate fate of these oils as foreign bodies is settled favorably they must remain under suspicion as poor therapeutic vehicles for intramuscular injection. The introduction of large doses in oil at long intervals gives a type of control which is inferior to that given by smaller doses spaced at shorter intervals. The latter is possible by oral treatment. Vaginal suppositories are useful chiefly when local effects on the vaginal mucosa are sought. The use of tablets or capsules of estrogens by mouth is an effective way to introduce adequate amounts of these hormones. The cost of the necessarily larger oral doses is no greater than that of the injection of therapeutically equivalent amounts when the cost of the injections is added to that of the hormone. With the greater convenience and more uniform control of symptoms, ad-

ministration by mouth is the recommended method. Doses vary widely. Minimum effective amounts for maintenance seem to be about 0.1 mg. (100 gamma, or 1000 units) of estrone. The maximum doses required to secure prompt relief from the more severe disturbances may run to 1.5 mg. (1500 gamma, or 15,000 units) in divided doses daily. Such large doses can be reduced gradually after the first few days or weeks.

The recommended plan of therapy is to use sufficient material to give relief, reducing the amount gradually but always keeping it high enough for real subjective satisfaction. Such a course may have to be continued for many years. At times it may be interrupted if symptoms are in abeyance, but it need not be interrupted for any reason save economy. The occurrence of flowing should not be the occasion for any alteration in dosage unless by trial there is greater comfort with more or less estrin at such times. It may be said, in summary, that menopause symptoms may be treated as due to the menopause even though flows persist.

When, however, there is the desire to restore menstrual rhythm or to improve fertility, the therapy should be based on an attempt to stimulate the ovaries.¹⁴ For this purpose the chorionic hormone (A. P. L.), derived from the urine of pregnant women, is not satisfactory. It does not stimulate the human ovaries, and its use does not initiate ovulation in women. Stimulation of ovarian functions may be attempted with some hope of success by use of two types of gonadotropic preparations: that from genuine pituitary, or that from the serum of pregnant mares. Preparations of these two types may be administered with safety hypodermically, in spite of the protein content of most of them. Local reactions to the injection of pituitary materials are unpleasant but usually not dangerous. Little benefit is to be expected from the use of a few doses. The active gonadotropic substances are water soluble, they act quickly and only for a few hours. Therefore the use of a series of doses given daily or on alternate days is the minimum that is promising. Such series will usually have to be repeated with a number of successive cycles before results are achieved. Since the ovaries are typically cyclic in all their activities, it is not surprising that cycles of stimulatory therapy are necessary. Cystic follicles may be produced²⁰ if continuous gonadotropic injection is practiced. Since follicular growth becomes more marked at the onset of a menstrual flow, it has seemed appropriate to commence the successive series of doses at the beginning of each flow. Such a period of treatments, amounting to 5 to 15 doses, is discontinued not later than the fifteenth day, the approximate time of a normal ovulation.

Though the hypodermic injection of even very large doses of gonadotropic extracts has not led to ovulation and the formation of corpora lutea, there is some evidence that intravenous injections will lead to ovulation.²¹ The use of pituitary extracts intravenously is still accompanied by some hazard because of their high protein content, but the employment of an extract from the serum of pregnant mares in highly concentrated form has the advantage here of being almost free from protein. If it is to be used intravenously it is probably wise to precede such injection by hypodermic doses to

stimulate the follicle to maturity. Also it is known that once a follicle has been made to ovulate, and the corpus luteum has been formed, pituitary stimulation is still required to sustain the action of the corpus luteum.²² Therefore it may be necessary to employ a few more daily doses of the hypodermic type to secure optimal luteal activity.

Reflection on these suggestions calls attention at once to the large number of doses required, and the need for a sustained effort for several months if results are to be maintained once they are secured. Even more one is led to wonder how the size of dose and the necessary number of doses may be estimated. At this point the vaginal smear technic is of help, for it enables the clinician to determine the extent of follicular secretion during the first two weeks of the cycle. The procedure is painless, takes little time, and is not expensive if done by someone who is handling a significant number of such patients. It is not adapted to general practice or occasional use. To determine the adequacy of luteal secretion, and to detect ovulation followed by corpus luteum formation, there are two possible methods: endometrial biopsy⁹ or pregnandiol estimation¹⁰ in 24 hour urine samples. Biopsies have disadvantages, especially in the danger of interrupting a possible pregnancy. Also, save in very experienced hands, the study of the tissue does not yield quantitative results. The estimation of pregnandiol excretion is better here, for the standards based on an available series of normals give some measure of the amount of this compound which should appear normally in the third and fourth weeks of the cycle.¹¹ The disadvantages include the collection of a series of 24 hour urine samples for a week or more, and a laborious and very costly chemical method. Perhaps the best that can be said of this urinary method and of the frequent use of biopsies is that their study has made possible an improved accuracy in diagnosis of anovulatory flowing, deficient action of progesterone, and improvement in these functions under therapy as outlined above.

Therefore the practitioner who is confronted with the need for treating hypofunction of the ovaries and who desires to attempt stimulation with gonadotropic extracts had best employ cycles of 5 to 15 daily doses, hypodermically, repeating the courses with the onset of each flow. If amenorrheic periods occur, the cycles of treatment may be carried out every four weeks until some flow occurs to mark a cycle of activity. For most hopeful results it remains necessary to subject such cases to semi-quantitative studies before and during therapy, by methods which are still available only in the well equipped endocrine-gynecological clinics.

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A NEW MATHEMATICAL METHOD FOR THE EVALUATION OF ENDOGENOUS INSULIN SECRETION*

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It has been said that insulin administration cannot be calculated by mathematical equations; that no one knows the exact amount of carbohydrate that will be metabolized by a given amount of insulin.¹

Probably every physician of experience in the treatment of diabetes mellitus has been puzzled at times to know how much insulin a given patient requires. We have all been confronted with the widely varied responses of different patients, as well as of the same patient at different times, to comparable doses of insulin.

This dissimilarity of response of different patients to comparable doses, or of the same patient at different times to the same dose of insulin, has defied satisfactory explanation largely because the factor of endogenous insulin secretion has been unpredictable. Because it has not been possible heretofore to estimate the physiological activity of the pancreas and other organs concerned with carbohydrate metabolism in terms of units of insulin, the administration of insulin has been largely an empirical procedure of trial and error, with the ever present danger of producing a hypoglycemia with too large a dose, or failing to accomplish the desired reduction of blood sugar with too small a dose.

We are all familiar with the repeated observation that patients in acidosis and coma "soak up insulin like a sponge," and heroic doses of insulin are required; yet we are often deterred from giving a single large dose by the fear of overdosage, and the desired result is unduly delayed by frequent repetition of small doses over a considerable period of time.

Given a patient with a fasting blood sugar of, say 300 mg. per 100 c.c.—how much insulin is it safe to give, and how small a dose will accomplish the desired result—namely, a rapid lowering of the blood sugar to normal limits?

Alexis F. Hartmann,² in 1925, described a mathematical calculation, by which, given a patient's body weight and blood sugar, the dosage of insulin can be calculated with sufficient accuracy so that, *theoretically*, the blood sugar can be reduced from any level to any point desired with a single dose of insulin. While the method has certain limitations which will be emphasized later, Hartmann's contribution has not received the notice and wide application it deserves.

It was while working with this method that we discovered a formula for measuring the approximate amount of insulin secreted in the body. This factor of endogenous insulin secretion is extremely important in any consideration of exact insulin dosage, yet, so far as we have been able to

* Received for publication July 19, 1938.

learn, nobody has heretofore devised any method of calculating the insulin secretion in a given patient. The purpose of this paper is to present a method of calculating insulin dosage, based on Hartmann's work, but which for the first time, takes into account the heretofore unpredictable factor of endogenous insulin. This method in our hands has, to a large extent, eliminated the empiricism and guesswork from insulin therapy.

We do not mean to imply that pathological physiology can be reduced to mathematical formulae. What we hope to accomplish is to elucidate a new method of measuring a physiological function which has no other yardstick. With due appreciation of its limitations and inaccuracies, we believe this method may be of vital importance in arriving at a better understanding of the physiology of diabetes mellitus. We present the method as a clinical experiment and hope that it will receive further trial by others.

Since a thorough understanding of Hartmann's calculation of insulin dosage is necessary to an understanding of its later application to the measurement of endogenous insulin secretion, the method will be described in some detail.

METHOD OF COMPUTING INSULIN DOSAGE, GIVEN THE BLOOD SUGAR AND THE BODY WEIGHT (See table 1)

According to Hartmann,² the weight of the body fluids and the soft tissues is taken to be $\frac{2}{3}$ times the body weight. Thus, if the body weight is 60 kg., the soft tissue is $\frac{2}{3}$ times 60 kg. = 40 kg. or 40,000 gm. (Allowance should be made for excess fat in obese patients.)

The concentration of glucose throughout the body, exclusive of the skeletal structures, is assumed to be the same as that of the blood. Thus, if the blood sugar is 0.35 per cent or 350 mg. per 100 c.c., then the total amount of glucose in the body is 0.35 per cent of the weight of the soft tissue, or $0.0035 \times 40,000 \text{ gm.} = 140 \text{ gm.}$

Similarly, if the blood sugar were 0.10 per cent or 100 mg. per 100 c.c., the total amount of glucose in the body would be $0.001 \times 40,000 \text{ gm.} = 40 \text{ gm.}$

Whence it is clear that to reduce the blood sugar from 0.35 per cent (350 mg. per 100 c.c.) to 0.10 per cent (100 mg. per 100 c.c.) it would be necessary not only to oxidize the excess sugar in the blood, but the total excess sugar in all the soft tissues, which in the above case would be 140 gm. — 40 gm. = 100 gm.

Putting it another way, to reduce the concentration of glucose from 0.35 per cent to 0.10 per cent the glucose to be oxidized = (0.35 per cent — 0.10 per cent) times the weight of the soft tissue or 0.25 per cent of 40,000 gm., whence $0.0025 \times 40,000 \text{ gm.} = 100 \text{ gm.}$

Since one unit of insulin will permit the oxidation of approximately two gm. of glucose, the amount of insulin required equals 100 divided by

two equals 50 units. Also, if the patient is given glucose intravenously, one additional unit is given for each two gm. of glucose injected.

The foregoing is, in principle and application, Hartmann's method of computing insulin dosage. However, such a calculation does not take into account the variable factor of how much endogenous insulin may be secreted at the same time insulin is administered parenterally.

We feel that allowance must be made for possible pancreatic insulin secretion if one is to avoid the possibility of dangerous hypoglycemic reactions, and that it would not be safe to give the entire calculated dose of 50 units at one time, and that therefore, pending evaluation of endogenous insulin, a smaller dose should be tried, say 20 to 30 units, plus an amount sufficient to cover the glucose injected.

It is true that patients in acidosis and coma secrete very little insulin. Nevertheless, all patients in coma are not necessarily total diabetics, and even though the foregoing calculation of insulin is based on 1 unit per

TABLE I*

Body weight	60*kg. = 60,000 gm.
Soft tissue $2/3 \times 60$ kg.	= 40 kg. = 40,000 gm.
Blood sugar	0.35%
Desired blood sugar	0.10%
Desired fall in blood sugar	0.25%
Total glucose to be oxidized	= 0.25% of soft tissue = $0.0025 \times 40,000$ gm. = 100 gm.
Insulin required	= $100 \div 2$ = 50 U
Infusion 10% glucose 600 c.c.	= 60 gm. glucose
Insulin to cover glucose given	= $60 \div 2$ = 30 U
Total insulin (single dose)	80 U

* Hartmann's calculation of insulin dosage.

2 gm. of glucose instead of 1.5 gm., there is grave possibility of overdosage if the pancreas happens to secrete more insulin than would be expected in a total diabetic. This is especially true in children in whom the margin of safety is much smaller than it is in adults, and in whom relatively small doses may cause hypoglycemia.

For example, in the case of L. M., aged six years (case 1), the blood sugar was 0.37 per cent before the noon meal, which contained 38 gm. of available glucose. The calculated insulin dosage necessary to reduce the blood sugar to 0.12 per cent, plus an amount sufficient to cover the available glucose in the noon meal, was 35 units. Not knowing as yet what to expect from the pancreas, we gave her only 20 units. Four hours later her blood sugar was 0.03 per cent or 30 mg. per 100 c.c. According to our subsequent calculation she had secreted over 20 units of insulin, which, together with the 20 units injected caused a dangerous degree of hypoglycemia.

DEFINITION OF THE TERM "ENDOGENOUS INSULIN"

Of course, in attempting to predict on a mathematical basis what the blood sugar will be after a given dose of insulin, one must realize that

there are many complicating factors which are potential sources of error. The constant ebb and flow of glycogen, the influence of other glands of internal secretion such as the pituitary, the effect of epinephrine on glycogenolysis, exercise, diets not all eaten or well tolerated, varying absorption of carbohydrate—all these are variables which influence the result. However, the net effect of the interplay of all these variable factors concerned with carbohydrate metabolism is to raise or lower the concentration of glucose a definite percentage.

The result, in blood sugar percentage, may be readily calculated as grams of glucose oxidized and (or) stored as glycogen, or added to the blood and soft tissues. It does not make any difference, so far as the concentration of glucose in the blood and other soft tissues is concerned, whether a given amount of glucose be partly or wholly oxidized or partly or wholly stored in the glycogen reservoirs, or partly oxidized and partly stored as glycogen. The number of grams of glucose above or below the original concentration is equivalent to the calculated effect of a corresponding amount of insulin, and may be expressed mathematically in terms of units of insulin on the basis of one unit of insulin per 2 gm. of glucose.

Our calculations indicate that the net effect of the functional activity of the liver, pancreas and other glands of internal secretion can be predicted with considerable accuracy, and that the resulting concentration of glucose in the soft tissues is the same as the concentration which might be expected to result from the utilization of a definite amount of insulin.

We therefore employ the term "endogenous insulin" as a quantitative expression of the sum total of the functional activity of all the factors concerned in carbohydrate metabolism as if the pancreas were the only factor involved.

Estimation of Endogenous Insulin. The fasting blood sugar is brought rapidly within the desired range (below 180 mg. per 100 c.c.) according to Hartmann's method (taking care to give somewhat less than the maximum calculated doses of insulin pending evaluation of endogenous insulin), after which the patient is started on a computed, weighed diet. The blood sugar is determined four hours after each meal and the maintenance insulin dosage and endogenous secretion are estimated as follows:

Example (See table 2)

Given a child weighing 18.75 kg., with a blood sugar of 225 mg. per 100 c.c., on a diet which contains 42 gm. available glucose in each meal (table 2).

In this problem the weight of the body fluids and soft tissues is $\frac{2}{3}$ (18,750 gm.) or 12,500 gm.

Assuming endogenous secretion to be zero, the effect of ingesting 42 gm. or 42,000 mg. of glucose would be to raise the blood sugar a definite amount. This is obtained by dividing the number of mg. of ingested glucose by the

number of hundred grams of soft tissue. Since the soft tissue weighs 12,500 gm. (or 125 hundred gm.) the calculated rise in blood sugar is 42,000 divided by 125 = 0.336 per cent. Adding this to the initial blood sugar of 0.225 per cent the calculated peak of the blood sugar curve is 0.561 per cent (still disregarding the presence of both exogenous and endogenous insulin).

Suppose we now desire to reduce the blood sugar from the estimated peak of 0.561 per cent to 0.121 per cent, a fall of 0.440 per cent. Then the total glucose to be oxidized would be $0.0044 \times 12,500 \text{ gm.} = 55 \text{ gm.}$ (The same figure would be obtained by computing the weight of glucose oxidized by reducing the blood sugar from the initial level of 0.225 per cent to 0.121 per cent and adding the number of grams of glucose ingested.)

The number of grams of glucose (55) divided by two gives the estimated insulin required.

TABLE II

Body weight, 18.75 kg.	18,750 gm.
Weight of soft tissue	12,500 gm.
Ingested glucose, 42 gm.	42,000 mg.
Initial blood sugar (b.s.)	0.225%
Expected rise in b. s. (42,000/125)	0.336%
Estimated peak b. s.	0.561%
Desired b. s.	0.121%
Desired fall in b. s.	0.440%
Total glucose to be oxidized (0.0044) (12,500)	55 gm.
Estimated insulin required 55/2	27½ U
Endogenous insulin	17½ U (?)
Insulin injected	10 U
Actual result b. s.	0.170%
Actual fall in b. s. (0.561-0.170)	0.391%
Actual total glucose oxidized (0.00391) (12,500)	49 gm.
Actual total insulin used (49/2)	24½ U
Actual amount of endogenous insulin (24½-10)	14½ U

Now, not having any previous calculations, we do not have any measure, as yet, of the functional activity of the pancreas. Therefore instead of injecting 27 units we inject only 10. The resultant blood sugar is 0.170 per cent, a drop of 0.391 per cent from the estimated peak, from which we calculate that the total amount of glucose actually oxidized, including soft tissue glucose plus ingested glucose, is $0.00391 \times 12,500 = 49 \text{ gm.}$

Dividing by two, the total insulin actually used (10 units injected plus endogenous insulin) was 24½ units, whence it is perfectly clear that the body must have provided approximately 14½ units of insulin.

This calculation is repeated for each meal on successive days until we have a very good idea how many units of endogenous insulin are available at certain times under the stimulus of a given amount of carbohydrate ingested. Provided one makes sure that all of the diet is taken, the output of endogenous insulin (after recovery from coma and ketosis) does not vary as much as one might expect. In fact the variation from day to day is

within sufficiently narrow limits that we soon strike an average estimate of the amount of endogenous insulin produced at different times during the day (table 6). By subtracting this amount from the total requirement we arrive at a very exact measure of the maintenance dosage of exogenous insulin required.

It has been surprising and exceedingly gratifying to us to find that we have repeatedly been able to predict and to obtain a blood sugar almost exactly what we had estimated it should be after a given intake of carbohydrate and an exactly calculated dose of insulin.

Case 1. L. M., aged five years 10 months, was first seen by M. M. on September 18, 1934, at which time she presented the picture of acidosis with air hunger, beginning coma, dehydration and malnutrition. Her urine contained acetone, diacetic acid and sugar four plus. She had been vaccinated against smallpox two weeks before and had developed vaccinia one week thereafter. The general health had always been good. There had not been any previous history or knowledge of diabetic symptoms. One maternal aunt had diabetes; otherwise the family and past histories were negative. She was admitted to the Childrens Hospital at 3:00 p.m., at which time the blood sugar was 0.37 per cent. She was given 15 units insulin subcutaneously plus 200 c.c. 10 per cent glucose (20 gm. glucose) and 10 units insulin intravenously. At 8:00 p.m., the blood sugar was 0.29 per cent. She was then given 20 gm. of glucose plus 20 units of insulin in 500 c.c. of Hartmann's solution subcutaneously. At 7:45 the next morning the blood sugar was 0.10 per cent. She was then started on a diet of P 50-F 100-C 75, containing 38 gm. available glucose in each meal. Two days later the diet was changed to P 50-F 75-C 90, containing 42 gm. available glucose. Blood sugars were taken before each meal and the insulin requirement and endogenous insulin secretion calculated. The results are tabulated in table 3.

TABLE III
(Breakfast)

Case 1 (L.M.)	9/19	9/20	9/21	9/22	9/23	9/24
Weight of soft tissue in gm.	12,800	12,800	12,400	12,400	12,400	12,400
Ingested glucose	38 gm.	38 gm.	42 gm.	42 gm.	42 gm.	42 gm.
Initial b. s.	0.100	0.420	0.480	0.400	0.340	0.215
Expected rise	0.297	0.297	0.338	0.338	0.338	0.338
Estimated peak	0.397	0.717	0.818	0.738	0.678	0.553
Desired b. s.	0.100	0.120	0.180	0.100	0.120	0.153
Desired fall	0.297	0.597	0.638	0.638	0.558	0.400
Estimated total glucose to be oxidized	38 gm.	76 gm.	79 gm.	79 gm.	69 gm.	50 gm.
Estimated amount of insulin required	19 U	38 U	39½ U	39½ U	34½ U	25 U
Estimated secretion of endogenous insulin	?	?	19½ U?	19½ U?	19½ U?	20 U?
Insulin injected	0	10 U	20 U	20 U	10 U	10 U
Actual result	0.370	0.210	0.225	0.095	0.140	0.100
Actual fall	0.027	0.507	0.593	0.643	0.538	0.453
Actual total glucose oxidized*	3½ gm.	65 gm.	73½ gm.	79.7 gm.	67 gm.	56 gm.
Actual total insulin*	1½ U	32½ U	36½ U	39½ U	33½ U	28 U
Insulin injected	0	10 U	20 U	20 U	10 U	10 U
Actual secretion of endogenous insulin*	1½ U	22½ U	16½ U	19½ U	23½ U	18 U

* Approximate.

TABLE III (continued)
(Dinner)

Case 1 (L.M.)	9/19	9/20	9/21	9/22	9/23	9/24
Weight of soft tissue in gm.	12,800	12,800	12,400	12,400	12,400	12,400
Ingested glucose	38 gm.	38 gm.	42 gm.	42 gm.	42 gm.	42 gm.
Initial b. s.	0.370	0.210	0.225	0.095	0.140	0.100
Expected rise	0.297	0.297	0.338	0.338	0.338	0.338
Estimated peak	0.667	0.507	0.563	0.433	0.478	0.438
Desired b. s.	0.120	0.110	0.125	0.100	0.140	0.100
Desired fall	0.547	0.397	0.438	0.333	0.338	0.338
Estimated total glucose to be oxidized	70 gm.	51 gm. -	54 gm. +	41 gm.	42 gm.	42 gm.
Estimated amount of insulin required	35 U	25½ U	27 U	20½ U	21 U	21 U
Estimated secretion of endogenous insulin	?	20 U ?	17 U ?	17 U ?	16 U ?	17 U ?
Insulin injected	20 U	5 U	10 U	4 U	5 U	3 U
Actual result	0.030	0.170	0.170	0.080	0.130	0.130
Actual fall	0.637	0.337	0.393	0.353	0.348	0.308
Actual total glucose oxidized *	81½ gm.	43 gm.	48.7 gm.	44 gm.	43 gm.	38 gm.
Actual total insulin *	40¾ U	21½ U	24½ U	22 U	21½ U	19 U
Insulin injected	20 U	5 U	10 U	4 U	5 U	3 U
Actual secretion of endogenous insulin *	20¾ U	16½ U	14½ U	18 U	16½ U	16 U

* Approximate.

The following points should be noted in table 3.

1. The morning after admission the morning blood sugar was 0.10 per cent. The patient had just recovered from coma. It was desired to see how much glucose she could oxidize without any exogenous insulin. She was therefore given her breakfast, containing 38 gm. available glucose, and insulin was withheld. On the basis of 1 unit of insulin per 2 gm. of glucose in her breakfast, her insulin requirement to keep her blood sugar at approximately 0.10 per cent was 19 units. The actual result was a blood sugar of 0.370 per cent, a fall of 0.027 per cent from the estimated peak; from which it was calculated she actually oxidized only approximately 3½ gm. of glucose. She therefore secreted approximately $1\frac{3}{4} \pm$ units of insulin. From then on she made a very rapid recovery and her endogenous insulin output in the morning varied between 16 and 24 units.

2. The same noon (September 19), because she had secreted so little insulin in the morning, she was given 20 units. The result was a drop from 0.370 per cent to a hypoglycemia of 0.03 per cent, which, as previously brought out, showed she actually oxidized (or stored in her glycogen reservoirs) approximately 81½ gm. of glucose, which was equivalent to 40¾ units of insulin, or 20¾ units more than was injected. Whence came this extra insulin except from an endogenous source? During the next five days the endogenous insulin available for the noon meal varied from 14 to 18 units.

3. That a basis of 1 unit of insulin per 2 gm. of glucose in calculating the insulin requirement, and that this method of computing endogenous

insulin is sufficiently accurate to be practical, are well shown in columns 9/22 and 9/23, in which the desired blood sugars on two successive days after breakfast were 100 and 120, and after dinner 100 and 140, and the actual results obtained were 95, 140, 80 and 130 respectively.

4. The blood sugars before breakfast shown in table 3 were consistently high. This was because the morning blood sugar could not be controlled satisfactorily without a midnight dose of insulin. It is well known that it is difficult to keep severe diabetics sugar free in the morning on three doses of insulin per day. According to Hartmann: "If the diabetes is very severe and approaches the 'total diabetic' state, the effect of the evening injection will be gone long before the next morning and the blood sugar may mount well beyond the threshold. In that case the patient cannot be kept entirely sugar free on three injections and must be given a fourth at midnight." In this patient a dose of insulin before supper, sufficiently large to keep the morning blood sugar below the renal threshold caused mild hypoglycemic reactions at about midnight. We are of the opinion that to apply our method of estimating the exact insulin requirements throughout the 24 hours, one should not only give four doses of insulin per day but also a midnight feeding. We did not do this because of lack of laboratory assistance at night. (No calculations for supper are presented because of this lack of any midnight blood sugar determinations to check the results. The procedure would be the same at 6:00 p.m. and at midnight as for the breakfast and dinner calculations.)

After sufficient blood sugar determinations three times a day to give a satisfactory estimate of the average amount of insulin secretion to be expected, blood sugars were taken only once a day, before breakfast, and the patient put on 10, 5 and 10 units before breakfast, dinner and supper.

The patient's glucose tolerance increased rapidly and by the thirteenth to the eighteenth day after admission the morning blood sugar varied from 0.155 per cent to 0.240 per cent, with an average morning blood sugar of 0.184 per cent.

She was discharged October 5, 1936, and readmitted two days later with an acute upper respiratory infection, temperature 105.0° F. This time she was in the hospital six days, during which time her diabetes was under control, with a morning blood sugar which varied from 0.085 per cent to 0.190 per cent, with an average of 0.136 per cent.

This case has been presented in considerable detail in order to explain the application of the method of estimating endogenous insulin.

Case 2 was one of severe diabetic coma in a 10 year old girl. All pertinent data relative to her clinical course are summarized in tables 4 and 5.

LIVER FAILURE DURING COMA

Table 5 is tabulated in a different form to show how the physiologic depression of carbohydrate oxidation and glycogenesis during coma may be expressed in terms of insulin deficit.

Date	Blood Sugar		Glucose (parenteral)			Insulin	
12/3	Noon	0.560	500 c.c. 10% glucose in saline (50 gm.) 500 c.c. 10% glucose in Hartmann's sol. (50 gm.)			40 U	
	4.00 p.m.	0.640				25 U	
	8.30 p.m.	0.400				30 U	
	12.00 m.	0.290				20 U	
						15 U	
	a.m.	Noon	p.m.	Diet			Insulin
12/4	0.040	0.260	0.220	C 150 P 47 F 40			25-20-10-5-5-5-R
5	0.040	0.140	0.175				10-15-10-5 R
6	0.330	0.160	0.090				
7	0.320	0.130	0.040				
8	0.180	0.060	0.090	C 180 P 60 F 60			
9	0.190	0.110	0.060				
10	0.240	0.105	0.110				10-7-10 R
11	0.300	0.200	0.090				
12	0.245	0.210		Lunch and noon insulin omitted;			10-7-12 R
13	0.260	0.140	0.070				tooth extracted
14	0.235	0.120	0.080				
15	0.210	0.085	0.140				
16	0.195	0.080	0.095				10-0-12 PZ
17	0.150	0.080	0.120				
18	0.170	0.145	0.200				15-0-12 PZ
19	0.200	0.350					
20	0.120	0.160	0.150	C 150 P 70 F 100			20 PZ
21	0.080	0.280	0.150				15 PZ
22	0.110	0.220	0.185				18 PZ
23	0.050	0.170	0.160				
24	0.095	0.240	0.225				22 PZ
25	0.050						
26	0.090						
27	0.050	0.070	0.080				
28	0.130	0.060	0.090				20 PZ
29	0.150	0.040	0.050				15 PZ
30	0.080	0.140	0.170				18 PZ
31	0.100	0.090	0.080				
1/1	0.100						16 PZ
2	0.080						
3	0.100	0.050	0.045				
4	0.140	0.180	0.170				
5	0.085	0.075	0.080				12 PZ
6	0.110	0.090	0.035				
7	0.120	0.075	0.150				
8	0.120	0.120	0.150				
9	0.080	0.140		Tooth extraction			
10	0.090	0.160	0.090				
11	0.080	0.150	0.110				
12	0.135	0.240	0.170				
13	0.080	0.090	0.105	Discharged			
14	0.130	0.160	0.160				
15	0.140	0.080					
16	0.065						

TABLE V
(Case 2)

Date	12/3				12/4					12/5
Hour	noon	4 p.m.	8 p.m.	12 m.	8 a.m.	1 p.m.	5 p.m.	8 p.m.	12 m.	4 a.m.
Gm. soft tissue	13,300									
Blood sugar	0.560	0.640	0.400	0.290	0.040	0.260	0.220	0.070*	0.125*	0.180*
Gm. G in diet					26	26		17.6	17.6	17.6
Gm. G parenteral	100				50					
Theoretical peak ^a	1.310	0.640	0.400	0.290	0.610	0.455	0.220	0.200	0.255	0.310
Insulin injected	65 U	30 U	20 U	15 U	25 U	20 U	10 U	5 U	5 U	5 U
Theoretical fall ^b	0.980	0.450	0.300	0.225	0.375	0.300	0.150	0.075	0.075	0.075
Theoretical result (x)	0.330	0.190	0.100	0.065	0.235	0.155	0.070	0.125	0.180	0.235
Actual result	0.640	0.400	0.290	0.040	0.260	0.220	?	?	?	0.040
Difference above x	0.310	0.210	0.190		0.025	0.065				
Difference below x				0.025						0.195
Gm. G above x ^c	41	28	25		3	8				
Gm. G below x ^d				3						26
Insulin deficit	20 U	14 U	12½ U		1½ U	4 U				
Insulin surplus				1½ U						13 U
Column number	1	2	3	4	5	6	7	8	9	10

^a Theoretical peak blood sugar if both endogenous and exogenous insulin were zero

$$= \text{initial blood sugar} + \frac{\text{mg. G administered}}{\text{no. of 100 gm. soft tissue}}$$

^b If endogenous insulin were zero, theoretical fall = $\frac{\text{mg. G oxidized by insulin injected}}{\text{no. of 100 gm. soft tissue}}$.

^c and ^d Gm. glucose remaining in blood and soft tissue above or below the amount theoretically present after oxidation by a given dose of insulin if the endogenous insulin were zero.

* Estimated.

? Unknown.

During the toxic stage of coma and acidosis there is a suppression of liver function as well as of pancreatic function, and the failure of large doses of insulin to lower blood sugar in accordance with theoretical calculations during coma is due to failure of the glycogen storage mechanism. The exact rôle of insulin in relation to both oxidation of glucose and glycogenesis is speculative. At any rate, as long as the glycogen storage function of the liver is suppressed by the toxemia incident to coma, it requires much larger doses of insulin to remove a given quantity of sugar from the soft tissues than it does after the patient recovers from coma and the liver function approaches normal.

The effect on the blood and other soft tissues, as far as the concentration of glucose is concerned, is the same whether a given number of grams of glucose be removed by glycogenesis or by oxidation, and, inasmuch as a given quantity of insulin will ordinarily cause the disappearance of a given quantity of sugar, the degree of failure of glycogen storage may be expressed in terms of insulin deficit.

This is strikingly illustrated in columns 1 to 10 of table 5.

In column 1 the theoretical effect of 65 units of insulin should be to lower the blood sugar from 0.560 per cent (or from the theoretical peak of 1.310

per cent after administration of 100 gm. glucose) to 0.330 per cent. The actual result was 0.640 per cent, a difference above the expected result of 0.310 per cent. This can only mean that 0.31 per cent more glucose should have been oxidized or stored in the glycogen reservoirs by the given dose of insulin than actually happened. In terms of grams of glucose this excess which was not oxidized or stored approximates 41 gm. (0.0031 times the weight of the soft tissue). In terms of insulin this represents a deficit of 20 plus units.

The next nine columns illustrate what happens as the patient recovers from coma and the liver function (and possibly the pancreatic function) improve. The insulin deficit drops in succeeding columns.

In column 4 the blood sugar was 0.290 per cent. The patient was given 15 units of insulin, which theoretically should oxidize 30 gm. of glucose, causing a drop of 0.225 per cent with an expected blood sugar of 0.065 per cent. The actual result was 0.040, a difference below the expected level of 0.025 per cent, corresponding to a reduction of 3 gm. more glucose than calculated (total 33 gm.), indicating that the liver, or the pancreas, or both had begun to resume their functions in carbohydrate metabolism. This striking improvement in liver function occurred during the first 12 hours.

Here then, we have a measure of carbohydrate metabolism of great prognostic significance.

In columns 7, 8, 9 and 10 the patient was given 10-5-5 and 5 units of insulin respectively at 5:00 p.m.—8:00 p.m.—12:00 midnight and 4:00 a.m. She was given 53 gm. of glucose (as milk) in divided doses at 8:00 p.m.—12:00 midnight and 4:00 a.m. As indicated by the asterisks, blood sugars were not determined after 5:00 p.m. until the following morning. Theoretically, with the ingestion during the night of 53 gm. of glucose and the administration of 25 units of insulin the blood sugar should have been higher the following morning (0.235 per cent) than it was at the beginning (0.220 per cent). The actual result was a blood sugar of 0.040 per cent, a reduction of 0.195 per cent more than expected, or the equivalent of 26 gm. more glucose metabolized than anticipated. This is a very significant finding and can only indicate one or both of two things—namely that either the storage reservoirs took up some or all of this glucose or there was a production of approximately 13 units of endogenous insulin. Perhaps the liver and pancreas both shared in the disposal of the extra 26 gm. of glucose. At any rate, the improvement in carbohydrate metabolism is exactly the equivalent of, and may be expressed mathematically as, an insulin surplus of 13 units.

Columns 4 and 5 in table 5 furnish additional evidence that 1 unit of insulin metabolizes approximately 2 gm. of glucose. From midnight to 8:00 a.m. the endogenous insulin was calculated to be plus $1\frac{1}{2}$ units to minus $1\frac{1}{2}$ units, or practically zero.

If one unit of insulin will metabolize 2 gm. of glucose when the endogenous insulin equals zero, then 15 units exogenous insulin (column 4)

should metabolize 30 gm. of glucose, producing a drop in blood sugar of 0.225 per cent and a theoretical result of 0.065 per cent. The actual result was 0.040 per cent, a drop of 0.250 per cent, which corresponds to 33 plus gm. of glucose. If from this is subtracted 3 gm. metabolized by $1\frac{1}{2}$ units of endogenous insulin, the amount actually metabolized by the 15 units exogenous insulin was 30 gm.

In column 5 the patient received 76 gm. glucose and 25 units insulin. The theoretical effect of 76 gm. glucose (if the endogenous insulin equals zero) should be to raise the blood sugar from 0.040 per cent to 0.610 per cent. The effect of injecting 25 units insulin should be to metabolize 50 gm. of glucose, producing a drop of 0.375 per cent and a theoretical result of 0.235 per cent. The actual result was 0.260 per cent, a drop of 0.350 per cent, which corresponds to $46\frac{1}{2}$ gm. of glucose. If to this is added 3 gm.

TABLE VI

Case 2. Average Amounts of Endogenous Insulin Secreted

Date	a.m.	Noon	p.m.
12/5/38	-4 U	11 U	?
6	24½ U	19 U	?
7	27 U	14 U	?
8	21 U	?	?
9	32 U	26 U	?
10	37 U	29 U	10 U
11	34 U	39 U	13 U
12	28 U	?	?
13	35 U	35 U	11 U
14	35 U	?	14 U
15	36 U	25 U	20 U
16	35 U	29 U	20 U

not metabolized due to liver failure (endogenous insulin deficit), the amount actually metabolized by the 25 units exogenous insulin was $49\frac{1}{2}$ gm.

These results, as well as those in columns 9/22 and 9/23 in table 3 demonstrate the great accuracy with which insulin dosage can be calculated and the resultant blood sugars predicted if proper allowance is made for endogenous insulin.

It should be emphasized, however, that this cannot be done accurately during coma, but only when the patient has recovered to a point where the endogenous insulin becomes stabilized (see table 6). Then, with sufficient calculations to give an average estimate of liver and pancreatic equilibrium in terms of units of endogenous insulin, subsequent blood sugars should approximate very closely the theoretical calculations.

Table 6 presents in tabular form the calculated amounts of endogenous insulin surplus after breakfast, lunch and supper from December 5 to 16 inclusive.

Column a.m. shows an average endogenous secretion of 26 units of insulin in the morning on December 6, 7 and 8 (hospital days four, five and

six) followed by an increase to an average of 34 units in the morning thereafter for a period of eight days.

Column noon shows an average of 15 units secreted in the afternoon on December 5, 6 and 7, increasing to about 30 units average from December 9 to 16.

Column p.m. shows the average night secretion after the midnight insulin dose was discontinued and the patient was on three meals a day to be about 12 units from December 10 to 14 and 20 units on December 15 and 16.

SUMMARY

Hartmann² showed in 1925 how the insulin requirement may be calculated, given the blood sugar and the weight of the soft tissue. However, Hartmann's work did not take into account the factor of endogenous insulin secretion; and allowance for pancreatic function in figuring insulin dosage has been based upon guesswork and trial and error.

By an elaboration of Hartmann's method we have shown how the amount of insulin produced in the body may be estimated, and how, by subtracting the average number of calculated units of endogenous insulin from the total insulin requirement, we obtain an accurate estimate of the amount of exogenous insulin required. By this method we are able to compute with considerable accuracy the dosage of insulin necessary to lower the blood sugar any amount desired.

This is possible only after a sufficient number of calculations to strike an average, and cannot be done while the patient is in coma. We have shown how the failure of carbohydrate metabolism during coma, due to liver and pancreatic failure, may be expressed in terms of insulin deficit, and have indicated how this may be used as a prognostic aid and a guide to subsequent insulin dosage.

CONCLUSIONS

1. Proper insulin dosage can be calculated according to mathematical formulae.
2. The method of calculating insulin dosage described by Hartmann is incomplete because it does not take into account the variable factor of endogenous insulin.
3. It is possible by the method we have described to estimate the physiologic activity of the liver, pancreas and other organs concerned with carbohydrate metabolism in terms of units of endogenous insulin.
4. The exogenous insulin requirement may be calculated by this method more accurately than has heretofore been possible.
5. The blood sugar concentration may be predicted by our method with considerable accuracy following the administration of a definite amount of glucose and an exactly calculated dose of insulin.

6. Our calculations provide evidence that the conception that 1 unit of insulin will metabolize 2 grams of glucose is approximately correct.

7. The depression of carbohydrate metabolism due to liver and pancreatic failure during coma may be expressed mathematically in terms of insulin deficit.

8. The improvement in carbohydrate metabolism after recovery from coma may be estimated and mathematically expressed in terms of increasing amounts of endogenous insulin.

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CLINICAL PICTURES ASSOCIATED WITH INCREASED BLOOD PRESSURE: A STUDY OF 100 PATIENTS *

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INTRODUCTION

UNTIL comparatively recently hypertension has been divided into the "renal" type (including glomerular nephritis and a few rarer disorders of the kidneys) and the "essential" type, the latter term being employed to indicate a rise in blood pressure not due to renal disease. Many clinicians have tended to accept essential hypertension as an entity due to a single but unknown cause. This concept is no longer tenable for two reasons. In the first place the demonstration by Goldblatt and his coworkers¹ that animals with experimental renal hypertension may present a clinical picture similar in all respects to that of essential hypertension in man has reopened the whole question of the distinction between renal and essential hypertension. In the second place there has accumulated during the past few years evidence which indicates that what was formerly called essential hypertension is not an entity, but is—like fever—a symptom which may be due to various causes. Some of these causes are known; others are entirely unknown; still others are partially known in the sense that they are suspected but their significance is unproved. Further knowledge in this field will appear more readily if the knowledge at present available can be sifted and classified. The purpose of this communication is to attempt a beginning toward the development of an etiologic classification of hypertension. Even though the evidence is much too incomplete to justify a final division of hypertension into various causes, a tentative division will perhaps be useful not only as a point of departure for a more accurate future classification but may also be of some immediate practical value in the treatment of patients.

In the discussion to follow no attempt will be made to review the extensive literature concerning hypertension. The report is concerned rather with a study of 100 patients having increased blood pressure. It will be shown that many of these patients fall into certain general groups, some of which are clearly defined, while others are still vague. Certain clinical features which require further study will be mentioned. Finally, an etiologic classification of hypertension which seems to be as accurate as can be developed in the present state of inadequate knowledge will be suggested.

* Read at the New Orleans meeting of the American College of Physicians March 28, 1939.

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This work was aided by grants from the Josiah Macy Jr. Foundation, the Rockefeller Foundation, and from Mr. Joe Werthan, Nashville, Tennessee.

SELECTION OF MATERIAL AND METHOD OF STUDY

The patients on whom this study is based have been observed either on the private wards or in the Out-Patient Department of the Vanderbilt Hospital. For the most part the study deals with cases seen consecutively. However, persons displaying elevation of the systolic pressure only and individuals with acute or chronic glomerulonephritis have been excluded. Furthermore, certain patients presenting unusual types of hypertension have been deliberately included for illustrative purposes, even though they did not fall within the consecutive series. All the patients dealt with have had at some time a systolic blood pressure of more than 150 mm. and a diastolic pressure of more than 100 mm. of mercury. In most of the individuals the elevation of blood pressure has been sustained but in a number the hypertension has been temporary.

All the patients have had complete histories and physical examinations, urinalyses, blood counts and determination of the non-protein nitrogen of the blood. Measurements of the rate of excretion of phenolsulphthalein, the concentrating power of the kidneys, the blood sugar and the basal metabolic rate were made in most instances. Glucose tolerance tests were done in many cases. At the beginning of the study the importance of the routine investigation of the urine for bacteria was not realized and this procedure was employed only when it seemed especially indicated. More recently cultures of the urine and in many instances search for bacteria in freshly voided urine have been made routinely. Measurements of the cholesterol content of the blood were made in a large percentage of the patients. Other diagnostic procedures have varied, depending on the indications in the individual subject.

After the findings in each patient had been summarized and tabulated an attempt was made to separate the cases into various syndromes. It should be pointed out again that such separation is not entirely justifiable at the present time and can only be defended on the grounds that it seems to us to represent the best that can be done in the present state of inadequate knowledge.

RESULTS OF CASE STUDIES

The chief findings are summarized in table 1.

A. The group as a whole exhibited few differences from similar groups studied by other authors. One somewhat surprising feature was the relative youthfulness of the patients. Our figure for the average age—49.3 years, indicated that most patients with increased blood pressure are middle-aged rather than elderly. Because of the method of selection of the patients, which involved the use of a large percentage of private patients, the figures relating to race have no significance. Our data indicating a preponderance of females over males in a ratio approximately 4:3 are practically identical with the findings of Fishberg.²

As regards the complications of hypertension the cerebral and cardiac manifestations were about equally frequent, the two most common symptoms being dyspnea and headache. If only serious manifestations are considered the phenomena dependent on cardiac disease were more frequent than those due to involvement of the nervous system. Although more than one-fifth

TABLE I
Summary of Clinical Manifestations on One Hundred Patients with Hypertension

		Neurogenic Group					Endo- crine Group	Metabolic Group		Renal Group					Congestive Heart Failure (Stau- ngedruck)		Mixed	Unclassified	Entire Group
		Psychoneurotic	"Stress and Strain"	Reflex (?)	Medullary	Increased Intra- cranial Pressure	Pituitary Basophilia	Menopause	Increased Blood Cholesterol	Increased Blood Uric Acid	Urinary Tract Ob- struction	History of Stone, Colic or Hematuria	History of Pyelitis	Marked Pyelone- phritis					
Number of cases		6	5	2	2	1	10	10	7	3	8	8	5	8	1	2	5	17	100
Mean age		48	52	55	14	71	51	48	60	38	57	51	42	34	40	56	51	52	49.2
Sex	Male	3	3	2	1	1	7	0	3	2	3	4	1	1	1	1	2	9	44
	Female	3	2	0	1	0	3	10	4	1	5	4	4	7	0	1	3	8	56
Previous Urinary Symptoms	Hematuria	1(?)	0	0	0	0	0	0	1	0	0	3	0	1	0	0	1	1	8
	Renal stone or colic	0	0	0	0	0	0	0	0	0	1	6	0	0	0	0	1	0	8
	Pyelitis	0	0	1	0	0	0	0	0	0	4	1	5	0	0	0	0	0	11
	Others*	0	0	0	0	0	0	1	1	1	4	0	5	8	0	0	4	5	29
Cerebral Apoplexy and crises Manifestations	Psychoneurosis	0	3	0	0	0	5	4	2	1	1	3	0	0	0	0	2	4	25
	Others	6	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0	1	13
		5	5	0	2	1	5	6	3	3	1	3	3	4	0	0	10	55	
Cardiac Symptoms	Angina pectoris	1	1	2	0	0	3	0	3	0	3	3	0	0	0	0	4	2	23
	Limited reserve	1	1	2	0	0	5	3	3	1	3	3	1	2	0	0	2	6	33
	Congestive failure	2	1	1	0	0	3	1	4	0	2	2	1	2	1	2	3	4	29
	Palpitation†	4	0	0	0	0	0	6	1	0	0	0	1	0	0	0	0	0	12
Vascular Retinitis‡	Absent	6	2	2	2	1	6	9	6	3	7	5	2	6	1	2	2	11	73
	Mild	0	1	0	0	0	4	1	1	0	1	3	1	1	0	0	2	3	18
	Severe	0	2	0	0	0	0	0	0	0	0	0	2	1	0	0	1	3	9
Cardiac Enlargement	Absent	2	1	1	2	1	4	5	3	1	1	3	2	2	0	0	0	4	32
	Slight	2	3	1	0	0	6	4	3	2	3	2	1	4	0	0	1	8	40
	Marked	2	1	0	0	0	0	1	1	0	4	3	2	2	1	2	4	5	28
Gallop Rhythm	Present	1	1	2	0	0	3	1	2	0	2	3	2	2	0	2	1	9	31
	Absent	5	4	0	2	1	7	9	5	3	6	5	3	6	1	0	4	8	69
Blood Pressure§	Highest	220	265	190	200	—	190	240	230	190	230	240	250	230	—	200	250	260	265
		120	180	110	140	—	120	135	140	124	130	130	170	170	—	120	150	160	180
	Lowest	130	150	170	190	—	140	150	150	145	140	170	190	150	—	172	140	150	130
		90	100	150	98	—	100	100	90	95	90	95	110	110	—	110	100	98	90
Mean	Mean	164	218	180	195	170	177	201	195	162	182	196	219	185	160	186	205	206	194
		104	134	105	110	100	107	120	105	108	114	114	132	126	100	115	119	124	118

of the patients had had symptoms pointing toward cerebral vascular crises (hypertensive encephalopathy) at some time in the past, only 9 per cent had had "strokes." Twenty-three patients had angina pectoris while 30 per cent had had congestive heart failure at some time. (The term congestive heart failure as employed in this paper is used to designate not only patients with systemic congestion but also those individuals who in the absence of

systemic congestion had had pulmonary engorgement as revealed by a history of orthopnea, a history of paroxysmal dyspnea, or by physical signs.) The most common objective abnormality was cardiac enlargement (66 patients). Although gallop rhythm was observed in 28 instances, chronic

TABLE I (continued)

Summary of Clinical Manifestations on One Hundred Patients with Hypertension

			Neurogenic Group					Endo- crine Group	Metabolic Group		Renal Group					Congestive Heart Failure (<i>Stau- ngedrucks</i>)	Mixed	Unclassified	Entire Group	
			Psychoneurotic	"Stress and Strain"	Reflex (?)	Medullary	Increased Intra- cranial Pressure				Fibritary Basophilia	Menopause	Increased Blood Cholesterol	Increased Blood Uric Acid	Urinary Tract Ob- struction					History of Stone, Colic or Hematuria
Renal Function	{ Normal { Impaired		5 1	2 3	1 1	2 0	7 7	9 1	8 2	1 6	3 0	6 2	6 2	4 1	7 1	7 7	1 1	3 2	9 8	67 31
Urine	{ Albumin	{ present { absent	0 6	2 3	1 1	0 2	0 1	2 8	0 10	4 3	0 3	1 7	2 6	1 4	0 8	1 0	2 0	3 9	8 7	27 73
	{ Pus	{ present { absent	0 6	0 5	1 1	0 2	0 1	1 9	0 10	0 7	0 3	4 4	4 4	1 4	1 7	0 1	0 2	2 3	2 15	16 84
Blood Cholesterol	{ Number of ob- servations { Average value		4 159	1 167	0 —	0 —	0 —	5 160	6 201	7 257	2 182	1 200	4 188	2 189	5 143	0 —	1 178	1 208	4 170	43 286
Leukocytosis	{ Present { Absent		0 6	3 2	1 1	2 0	1 0	0 10	1 9	2 5	0 3	4 4	3 5	4 4	1 4	0 1	1 1	0 5	4 13	4 73
Anemia	{ Present { Absent		0 6	0 5	0 2	1 1	0 1	0 10	4 6	0 7	0 3	2 6	0 8	3 2	2 6	0 1	0 2	0 5	2 15	14 86
Uremia	{ Present { Absent		0 6	2 3	0 2	0 2	0 1	0 10	0 10	0 7	0 3	4 4	0 8	1 4	0 8	0 1	0 2	1 4	4 13	12 88
Urine Cultures	{ Not taken { Sterile { Colon bacillus { Streptococci { Other bacteria		3 3 0 0 0	3 2 0 1 2	1 0 0 0 1	2 0 0 0 0	1 6 0 1 0	6 2 0 1 0	3 7 0 0 0	3 2 0 2 0	1 1 0 4 1	1 2 2 2 1	1 2 2 2 1	0 0 3 3 1	0 — — 6 —	1 — — 0 —	1 1 1 0 0	1 2 1 2 5	4 6 0 2 3	32 29 13 24 9

* This does not include a history of gonorrhea and does not include frequency and nocturia except when very marked.

† This includes only cases in which palpitation was one of the main complaints and does not include palpitation associated with premature beats.

‡ This includes hemorrhage, exudate and papilledema.

§ In compiling the table only the average blood pressure for each patient was considered.

|| Renal function was considered as impaired when the maximum specific gravity as determined by Fishberg's procedure² was below 1.022 or the excretion of phenolsulphonephthalein was less than 50 per cent in two hours.

¶ Patients with only a few white blood cells per high power field were not included.

** This group included individuals with a leukocyte count of ten thousand or more.

†† Subjects with hemoglobin values of less than 12 grams per cent were classified as anemic.

‡‡ A few of the cultures were made directly from the ureters or on freshly voided specimens after carefully washing the genitalia, but most of them were catheterized specimens from the bladder.

auricular fibrillation was present in only two subjects. (We had expected to find a much higher instance of this arrhythmia.)

Although the cardiac and the cerebral disorders displayed by the patients were in the main the results of increase in blood pressure, the situation was quite otherwise in regard to the symptoms referable to the urinary organs.

In compiling the data we did not include those minor urinary symptoms such as mild degrees of polyuria, frequency and nocturia, which are so commonly the result of cardiovascular disease. Most of the patients did not have more serious urinary symptoms at the time of observation, but careful analysis of their histories revealed significant symptoms referable to the urinary tract in a fairly large percentage. Thus, 10 patients had had gross hematuria at some time in the past, seven individuals gave a typical story of renal colic, five subjects had had pyelitis. Five patients had either passed a kidney stone or had had a diagnosis of renal stone made at some time. Twenty patients had had in the past either dysuria, marked frequency of urination or both. In regard to these symptoms referable to the urinary tract, two points should be emphasized: First, that although quite definite they were not impressive and were not mentioned by the patients except in response to careful questioning; and second, these symptoms were of such a nature that they could not have been the result of hypertensive vascular disease. Whether or not such symptoms were in any way related to the causes of the hypertension will be discussed later.

Fifty-four of the 100 patients had a family history of some type of cardiovascular disease. Our histories in this regard were not particularly carefully taken and it is probable that the actual incidence of cardiovascular disease in the families of the hypertensive patients was considerably higher than this.

A note was made of the complexion in all cases. Twenty-eight subjects were ruddy and 17 were pale, the remaining individuals being normal in this respect. Most of our subjects did not therefore conform to either the red or the pale groups of Volhard.

The body habitus was recorded as thin (21 subjects), stocky (23 subjects), generalized obesity (15 subjects), obesity confined mainly or entirely to the trunk (11 subjects), or normal (29 subjects). Aside from that group of patients with a buffalo type of obesity these figures for the physical types are not particularly impressive and are probably not very different from what would be observed in a group of non-hypertensive patients with the same age distribution.

One interesting point was the rarity of anemia. No patient in the series had severe anemia and in only 14 instances was the hemoglobin less than 12 grams per cent. A leukocyte count of 10,000 per cubic millimeter or more was observed in 27 patients.

Pyuria (varying in degree from numerous white blood cells per high power field to clumps of white cells) was present in 19 instances. Many other patients showed occasional white blood cells which were not considered as significant.

Urine cultures were made in 68 patients. No bacteria were found in 31 instances. Positive cultures were obtained in the remainder. The significance of this finding will be discussed below.

Although when considered as a whole these 100 patients had little in common except increase in blood pressure plus a tendency toward symptoms brought about by the usual consequences of hypertension, a survey of the individual case records revealed a number of different clinical patterns, some of which were observed frequently while others occurred rarely. Granting that similarity in clinical features does not necessarily indicate identity in etiological background, these patterns seem to merit more detailed consideration.

B. Syndromes Associated with Hypertension. These fall into several groups, each with one or more subdivisions.

1. *Neurogenic.* This term is used to signify that the factors responsible for the increase in blood pressure appear to operate through the nervous system.* Five different subgroups were noted.

(a) *Psychoneurotic.* Six patients showed the clinical features of neurosis and resembled the cases described by Ayman.³ Anxiety was pronounced in each. Palpitation was the outstanding complaint in four subjects. Intermittent tachycardia was a striking feature. Superficially, the clinical features in these patients resembled those of thyrotoxicosis but all had normal metabolic rates. The blood pressure was much affected by emotion and showed marked decline with reassurance. Sedatives were especially beneficial in these subjects. The symptoms consisted mainly in palpitation and the usual symptoms of neurosis. However, cardiac enlargement was present in four patients. The blood pressure exhibited marked fluctuation according to the emotional state. Four of the six patients had a definite family history of hypertension.

These findings led us to suspect that in a person predisposed by heredity a severe and more or less continuous disturbance in the higher nervous centers may affect the sympathetic nervous system in such a way as to produce an increase in blood pressure, which, although at first intermittent, may later become permanent.† Granting that in cases such as these the psychoneurotic state is probably not the only etiologic factor, it is certainly an important one and therapy should be directed primarily toward it. That such therapy may at times be extraordinarily effective is illustrated by case 1. (See appended case records.)

(b) *"Stress and Strain."* Five patients displayed a syndrome resembling in some respects that of the previous group. Each of these individuals developed hypertension while living under conditions of unusual

* Such a statement does not imply that the rise in blood pressure is necessarily mediated through the vasoconstrictor nerves. Conceivably neurogenic hypertension could be induced through the effect of the nervous system on the endocrine glands, on the renal blood vessels, or by some unknown means. In this paper we are not concerned with the question of the exact mechanisms whereby the increase in blood pressure is produced but rather with the morbid states which set off or aggravate such mechanisms.

† A patient's knowledge that his blood pressure is increased frequently leads to the development of a psychoneurotic state. The problem as to which was primary in our cases could not be solved. From a practical point of view it makes no difference. The abnormal emotional state in these six patients was certainly an aggravating factor if not the primary cause and therapy directed toward it caused marked improvement.

mental and emotional strain. Three had hypertensive encephalopathy. Two developed malignant hypertension and died of uremia. Another subject who had severe symptoms (including a blood pressure of 300/200, cerebral crises and vascular retinitis), was diagnosed as malignant hypertension but improved markedly after the conditions responsible for the mental stress had been eliminated and two years later remains practically free of all symptoms with only moderate elevation of blood pressure.

Whether severe mental strain can initiate hypertension is debatable. In favor of an affirmative answer is the case of a 33-year old male (not included in the series) whose blood pressure was found to be 180/110 immediately after two weeks of intensive work under severe stress. When he reduced his working hours to 10 or 12 per day his blood pressure declined in a few days to 118/78. During repeated observations for 10 years before and for six years after this episode his blood pressure has always remained normal.

If it be assumed that a prolonged period of mental stress can produce elevation of blood pressure, one can best account for the development of malignant hypertension in some subjects within this group by assuming further that the increased blood pressure induces changes in the renal blood vessels, thereby causing further rise in blood pressure and inducing a vicious cycle.

Case 2 is illustrative of the condition which, for want of a better name, we have termed the "stress and strain" type of hypertension.

(c) *Reflex*. During anginal attacks the blood pressure is usually elevated. This is not simply a result of pain for Levine and Ernste⁴ showed that severe pain due to other causes was not attended by a similar rise in blood pressure. Alam and Smirk⁵ found that exercising ischemic skeletal muscles caused a well marked increase in blood pressure which set in before pain occurred. The effect was apparently of reflex nature because under the conditions of the experiments the venous return from the ischemic muscular tissue was blocked. One occasionally observes patients with hypertension who, following coronary thrombosis and disappearance of the previous anginal attacks, have a normal blood pressure for months or years. (We are not referring here to the acute decline in blood pressure during the first few days but to the persistent decline, which remains after the patient has recovered entirely.) In our series of 100 hypertensive individuals there were two such patients. One of them was of especial interest because his blood pressure had been followed for a number of years and had not become elevated until he developed angina pectoris. Following myocardial infarction he had no more anginal attacks and his blood pressure has remained within normal limits for 18 months since.

The facts mentioned in the preceding paragraph can be accounted for if one assumes that an ischemic area in the heart may cause a reflex rise in blood pressure. Against such an assumption are the following points:

(1) Many patients with angina pectoris do not have hypertension.

(2) A reflex rise in blood pressure induced by oxygen deficiency in the heart has not to our knowledge been demonstrated in experimental animals. The evidence that sustained hypertension may be brought about by a reflex from the heart is therefore entirely inconclusive. Even if such a mechanism does exist, this type of hypertension will remain difficult to recognize because it can only be diagnosed in patients whose blood pressures have been followed before and after coronary thrombosis. We are certainly not justified in assuming that this mechanism is operative in all patients who have sustained increase in blood pressure and are subject to attacks of angina pectoris, because the latter disorder is of fairly frequent occurrence in patients with any type of hypertension.

An instance of hypertension which may conceivably have been due to reflex from the heart is illustrated by case 3.

(d) *Medullary.* Certain disorders which cause injury to the brain stem may be accompanied by hypertension. Such was the case in two of our patients. One was a boy of 20 with acute poliomyelitis and a blood pressure of 200/92 (case 4). We have likewise observed two patients with post-diphtheritic paralysis whose blood pressures were elevated and declined to normal as the paralysis disappeared (cases 5 and 6). Whether in such instances the hypertension is brought about directly, through irritation of the vasomotor centers and the brain stem, or whether some other mechanism is concerned is uncertain.

(e) *Increased Intracranial Pressure.* One patient in our series had an elevation of blood pressure associated with a skull fracture. Such cases are quite common. Less frequently conditions which cause more persistent elevation of the intracranial pressure may induce hypertension. Occasionally a vicious cycle is set off, hypertension induced by any means leading to increased intracranial pressure, and this in turn causes further rise in blood pressure. The dramatically beneficial results of spinal puncture in certain patients with eclampsia can probably be ascribed to the breaking up of such a cycle.

2. Endocrine Group.

(a) *Pituitary.* Ten of the 100 patients presented features suggestive of pituitary basophilia (Cushing⁶). Each of the individuals had obesity involving the trunk with relatively slender extremities. Each had a florid complexion and a short neck. Four subjects had hyperglycemia, three had skeletal decalcification and one had sciatica. Seven of the 10 subjects were males. None of the patients had malignant hypertension. Although symptoms referable to the heart and brain were common there was no history of symptoms referable to the kidneys. As a rule both the systolic and diastolic pressures were less elevated than in most of the other groups. Of four patients treated with deep roentgen-ray therapy over the pituitary gland only one showed marked improvement (case 7). On theoretical

grounds it would seem that reduction of weight should have an especially beneficial action in obese patients with pituitary hypertension for there is reason to believe that restriction in caloric intake may depress the activity of the basophilic cells of the anterior lobe of the hypophysis.

(b) *Menopausal*. Ten subjects were included in this group because their increase in blood pressure set in concurrently with the onset of the menopause. The relationship of the increase in blood pressure to the cessation of menstruation seemed fairly definite in three patients who exhibited rise in blood pressure following induction of the menopause by artificial means. However, of the seven patients with hypertension developed at the time of spontaneous menopause, six were definitely psychoneurotic and the increase in blood pressure in these subjects could just as readily have been ascribed to this factor as to the menopause. When considered as a whole this group was characterized by the absence of retinal changes, the frequency of palpitation, the occurrence of anemia—a symptom which was quite unusual in most of the hypertensive patients—and a relatively mild course. Prolonged treatment of two patients who were not psychoneurotic with large doses of the female sex hormone was without effect on the blood pressure. However, the patients in this group who are psychoneurotic are usually benefited by relieving their symptoms by sedation or substitution therapy.

3. *Metabolic Group.*

(a) *Increased Blood Cholesterol*. In seven patients the only abnormality found which could reasonably be related to the genesis of the hypertension was increase in blood cholesterol. These patients were somewhat older than those in the other groups; angina pectoris was frequent; general arteriosclerosis was outspoken; congestive heart failure was common; the pulse pressure was relatively high; the aortic knob was prominent in fluoroscopic examination. These points led to the suspicion that the increase in blood pressure in these patients might have been the result of atheroma of the renal arteries with consequent impairment of the renal blood flow and the induction of a mechanism corresponding to that responsible for the experimental hypertension caused by artificial narrowing of the renal arteries (Goldblatt, et al.¹). The findings in the only patient within this group who was subjected to necropsy were compatible with this view (case 8). Four of the patients in this group had diabetes, two had hypothyroidism. In view of the possible relationship of the increase in the blood cholesterol to the genesis of the hypertension it would be of interest to observe the effect of the administration of thyroid to the patients. We have not as yet made any observations on this point.*

(b) *Increased Blood Uric Acid*. One patient had outspoken gout with well marked elevation of blood uric acid. Two other subjects had slight

* Since this paper was written we have observed a number of additional patients with hypertension, hypercholesterolemia, and evidence of arteriosclerosis. It seems probable that sclerosis of the larger renal arteries is the most common cause of hypertension developing after the age of fifty-five.

elevations of the uric acid content of the blood without other signs of gout. Whether the increase in blood pressure in these three patients could have been related to uric acid deposits in the kidneys is uncertain.

4. *Renal Group.* Thirty patients had evidence pointing toward some type of kidney disease either at the time of observation or in the past. These subjects were divided into five sub-groups:

(a) *Urinary Tract Obstruction.* Of the five females in this sub-group one had a carcinoma of the ovary, one had ovarian cyst, two had uterine myomata and one had had a stricture of the ureter several years previously. Of the three males one had benign hypertrophy of the prostate, a second had urethral stricture and later developed carcinoma of the prostate, and a third had chronic prostatitis. The average age of the eight patients was 55 years. Four of the subjects had pyuria during observation. Anemia was present in three instances and leukocytosis in four. The hypertension was relatively mild and none of these eight subjects had evidence of malignant hypertension. Vascular retinitis was present in only one individual and was mild in this patient. Urine cultures were positive in five of the six instances in which they were made, the chief organisms being the colon bacillus and a streptococcus. Eradication of the infection with sulfanilamide was followed by marked decline in blood pressure in one patient (case 9), and questionable benefit in the only other subject in whom this procedure was carried out.

Four of the patients with urinary tract obstruction had nitrogen retention. These were the only instances in the entire series of 100 hypertensive patients in which renal insufficiency occurred in conjunction with relatively little hypertension. All of the other subjects with uremia had a more marked elevation. This point may possibly be of some diagnostic value.

Only one of the patients in this sub-group died while in the hospital. The autopsy finding of marked unilateral pyelonephritis furnished strong evidence for the view that the urinary tract obstruction was responsible for the elevation of blood pressure (case 10).

(b) *History of Stone, Colic or Hematuria.* Of the eight patients in this sub-group six had a typical history of renal colic and three had had unexplained hematuria at some time in the past. There were four males and four females, the average being 51 years. Vascular retinitis of mild degree was present in three patients but none had severe retinitis. The increase in blood pressure was relatively mild, there being no instances of malignant hypertension. At the time of observation four of the patients had pyuria and three had leukocytosis. The pyelograms were abnormal in two of the three instances in which they were made. None of the subjects had nitrogen retention. Urine cultures were positive in five of the seven patients, showing colon bacillus in two cases, streptococcus in two and staphylococcus once. Attempts to disinfect the urinary tract were not made in any of the patients.

(c) *A typical history of pyelitis* was given by five subjects, four of them

being females. In two of the patients the pyelitis began during pregnancy. The average age in this sub-group was relatively low, being 42 years. Vascular retinitis was absent twice, mild in one patient and severe in two others. The latter two subjects had malignant hypertension. Renal function was impaired in only one of the five patients, this individual later dying of uremia. Albumin was absent from the urine of four of the five subjects and pus was found in the urine at the time of observation in only one instance. Three of the five patients were anemic. Urine cultures were positive in each of the four subjects in which they were made. Colon bacilli were found three times, streptococci three times and staphylococci once. Attempts to disinfect the urinary tract were not made. (Case 11 represents an example of hypertension occurring in a patient with a history of pyelitis.)

Peters⁷ has recently pointed out the importance of pyelitis in relation to the so-called toxemias of pregnancy. The correctness of his view that a relationship exists between these disorders is supported by two of our patients who had pyelitis during pregnancy and who developed increase in blood pressure at this time. Both of these individuals were originally diagnosed as having "toxemia of pregnancy." The findings in the other three patients in the group suggest that the occurrence of hypertension in association with pyelitis is by no means limited to pregnancy. The situation in regard to these five patients may be summarized by saying that they had "burnt out" pyelitis masquerading as "essential" hypertension.

(d) *Masked Pyelonephritis.* This term is applied to eight young subjects with an average age of 34 years, of whom seven were females, who presented a picture somewhat similar to that described by Longcope,⁸ but differing from that of his subjects in that the symptom-complex simulated "essential" hypertension rather than chronic glomerular nephritis. These patients differed from those in the previous sub-group in that they did not give a definite history of pyelitis. The symptoms were vague and mild. Five of them complained of mild pain in the back which usually appeared with fatigue in the latter part of the day. Four of them had had either frequency, burning or nocturia at some time in the past but these symptoms had not been pronounced and were usually mentioned only in response to careful questioning. Only one of the eight subjects had had hematuria. The increase in blood pressure had been discovered accidentally in most of the subjects. Cerebral symptoms were either absent or of minimal severity. None of the eight patients had angina pectoris, although four had some cardiac enlargement, two had dyspnea on exertion and two had congestive heart failure. Vascular retinitis was present in two subjects and severe in one of these who had the typical picture of malignant hypertension. Albumin was absent from the urine in all instances. The initial routine examination of the urine showed pyuria in only one case, but repeated examinations of catheterized specimens revealed occasional clumps of white blood cells in most of the others. These patients tended to have

an intermittent slight fever. Mild anemia occurred in two of the eight subjects while four had leukocytosis. Nitrogen retention was absent in all instances. Pyelograms were made in four patients and all were either abnormal or revealed changes of doubtful significance. Urine cultures yielded streptococci in six patients and colon bacilli in the other two.* Attempts at disinfection of the urine were made in five instances. Distinct benefit was observed twice and questionable benefit in the remaining three subjects. The two patients who seemed to be improved the most are illustrated by cases 12 and 13. Our limited experience up to the present time does not justify any conclusions as to the value of therapy of this type. Conceivably the decline in blood pressure observed may have been coincidental. It is also possible that more prolonged and more intensive therapy might be beneficial in a larger percentage of the cases. These questions are still under investigation.

(e) *One patient had coarctation of the aorta.* He has been classified in the renal group because the investigations of Rytand⁹ have shown that experimental narrowing of the aorta above the level of the renal arteries causes hypertension, while the same procedure carried out immediately below the renal arteries produces no rise in blood pressure. Rytand also showed that hypertension could be produced by constricting the aorta between the renal arteries. If the lower kidney was removed the animals did not develop hypertension. His observations seem to indicate that the mechanism described by Goldblatt is responsible for the increase in blood pressure which occurs in the upper part of the body in patients with coarctation of the aorta.

These observations concerning the frequency of renal disorders in patients with "essential" hypertension are in accord with the studies of Schroeder and Steele,¹⁰ who found that a large percentage of hypertensive patients had abnormal pyelograms.

5. *Congestive Heart Failure.* Although cardiac decompensation, when setting in acutely, is usually accompanied by hypotension, an increase in blood pressure frequently occurs when heart failure develops slowly. In such instances the blood pressure declines as improvement occurs. The mechanism of this increase in blood pressure (*Stauungshochdruck*), which appears in certain patients with congestive heart failure is unknown. Various possible factors have been discussed elsewhere.¹¹

In two of our 100 hypertensive patients the blood pressure declined to normal as improvement in the cardiac condition occurred. No cause—

*In the absence of gross infection urine cultures must be very carefully evaluated. Voided urines collected under aseptic conditions in normal men yield organisms in over half the cases, which bacteria are apparently normal inhabitants of the anterior urethra. Catheterized urine from both men and women may contain bacteria although infection does not exist. To be certain that infection is present in the kidney one should grow bacteria from urine obtained directly from the kidney. Demonstration of the organism by direct smear is of definite aid in diagnosis. Since the concentration of urea in urine is often high enough to be bacteriostatic one should always inoculate the media directly after obtaining the specimen. Streptococci which occur in the urine are often partially anaerobic and grow better in poured blood plates or anaerobic broth.

other than congestive failure—for the hypertension could be found in either subject. Several other patients who were classified in other groups displayed decrease in blood pressure—but not to normal levels—as heart failure disappeared. It would seem that cardiac decompensation is frequently an aggravating cause of hypertension but is only occasionally the primary factor.

6. *Mixed Group.* Many of the patients who were considered as belonging to the various groups which have been discussed had evidence of more than one cause for the increase in blood pressure. In most instances one factor seemed to be the chief one and the subjects were classified accordingly. There were four patients who displayed more than one possible cause of the increase in blood pressure without predominancy of any particular factor. One other patient (case 6) developed hypertension in association with post-diphtheritic paralysis. Several months after her blood pressure had returned to normal she developed acute pyelonephritis and associated with this her blood pressure again became elevated. These subjects were placed in the "mixed" group.

7. *Unclassified Group.* As has been mentioned, the purpose of this study was to attempt a beginning at the development of an etiologic approach to the problem of hypertension. Consequently, an effort was made to classify each patient according to some factor which might conceivably be responsible for the increase in blood pressure, even though we realized clearly that the evidence justifying such a classification was decidedly inadequate. Even when rather elastic criteria were used there were still 17 patients who could not be classified. If we had adhered to rigid criteria and had insisted that no patient be placed in a group unless the cause of the increase in blood pressure was clearly established, the unclassified group would have been much larger and would have included most of the patients.

DISCUSSION

On the basis of the data which have been presented, of our experience with other hypertensive patients which were not included in the present series, and of reports in the literature, the following classification of hypertension is suggested as representing a working approach toward an etiological concept of this disorder:

CLASSIFICATION OF HYPERTENSION *

I. Neurogenic

A. Psychogenic

1. Psychoneurotic †
2. Stress and strain

* This does not include patients with elevation of the systolic pressure only.

† These conditions are likely causes of elevated blood pressure in children or young adults.

B. Medullary

1. Diphtheria †
2. Poliomyelitis †
3. Encephalitis †

C. Increased intracranial pressure †

D. Reflex

1. Carotid sinus ‡
2. Aortic depressor nerves ‡
3. Ischemic muscle
 - a. Cardiac
 - b. Skeletal

II. Endocrine

A. Pituitary (basophilic hyperplasia—Cushing's syndrome)

B. Adrenal

1. Medullary—adrenalin (pheochromocytoma) ‡
2. Cortical tumors

C. Ovarian

1. Menopause
2. Arrhenoblastoma

III. Renal

1. Acute and chronic glomerular nephritis †
2. Obstruction to urine flow †
 - (a) Congenital anomalies †
 - (b) Ureteral stricture †
 - (c) Urethral obstruction
 - (d) Pelvic tumors
 - (e) "Spinal" bladder
3. Urinary tract infection
 - (a) Pyelitis †
 - (b) Pyelonephritis (classical or masked) †
4. Diseases of renal arteries
 - (a) Renal atheroma (large and small arteries)
 - (b) Arteriolar sclerosis §
 - (c) Infarcts of kidney
5. Tumors of kidney
 - (a) Wilms tumor †
 - (b) Other tumors

*Prinzmetal and Oppenheimer¹² showed that the gradient between the pressures in the brachial and digital arteries is abnormally great in hypertension of this type because adrenalin causes constriction of the medium sized arteries.

†These conditions are likely causes of elevated blood pressure in children or young adults.

‡Demonstrated in animals but not in man.

§Although arteriolar sclerosis is probably initiated by hypertension in most instances it tends to cause a further rise in blood pressure.

6. Coarctation of aorta ‡ (see footnote on previous page)

7. Renal calculi

IV. Metabolic

1. Hypercholesterolemia (renal atheroma?)

2. Gout (uric acid deposits in kidneys?)

V. Congestive heart failure

VI. Mixed and unclassified causes of hypertension

In regard to this classification certain points should be emphasized:

(1) No attempt has been made to distinguish between underlying and aggravating causes of hypertension. Thus, glomerular nephritis is clearly an underlying cause, while mental stress and strain is in all probability an aggravating or precipitating cause. Many of the conditions which have been listed seem to produce hypertension only when they occur in predisposed subjects. Thus, mild renal infections seem to cause hypertension in some patients while more severe renal infections in other subjects may be accompanied by normal blood pressure. The difference may be ascribed to "predisposition," but this is simply substituting a name for an explanation, for we do not know what predisposition is, although we assume that it operates in some way through heredity. Until more is known about this question it seems wise to include in an etiological classification all factors which seem to produce hypertension, even though some of them may not initiate the disorder but serve only to intensify it. In this paper interest is centered primarily on those etiological factors which can be treated, and from this standpoint it makes no difference whether a given condition is underlying or aggravating, provided that treatment directed toward it will produce benefit.

(2) The classification which we are suggesting is concerned with conditions tending to lead to hypertension but does not deal with the mechanism whereby the increase in blood pressure is brought about. In spite of the important advances made within the past few years, the pathogenesis of hypertension remains obscure in many patients. There is some evidence that what we have called neurogenic hypertension may actually operate through the kidney. Thus, Braun¹³ found that the experimental hypertension produced by the intracisternal injection of kaolin can be alleviated by renal denervation. It is also likely that most types of endocrine hypertension may operate through some renal mechanism for it has been shown that integrity of the adrenal cortex is necessary in order to produce hypertension by means of renal ischemia (Goldblatt,¹⁴ Blalock and Levy¹⁵). Another unsolved problem relates to the means whereby obstruction and infection in the urinary tract induce a rise in blood pressure. The question as to whether such conditions act through interference with blood supply to the kidney is still unanswered. At the present time no final conclusion can be drawn concerning the exact mechanism of the various types of renal hypertension,

or regarding the possible relationship of extra-renal hypertension to renal pressor mechanisms.

(3) In the classification mentioned above reference to the toxemias of pregnancy has been deliberately omitted. Peters⁷ has shown that a large percentage of such patients have pyelitis. Even in the absence of infection it is probable that hydronephrosis due to pressure on the ureters from the enlarged uterus may induce a rise in blood pressure. In still other instances pregnancy may occur in a woman already having chronic glomerular nephritis or some other cause of hypertension. Whether endocrine disturbances play a rôle in the production of hypertension during pregnancy is still unknown. Until further evidence is available it seems wise to regard hypertension during pregnancy not as a disease entity but as similar in origin to hypertension appearing in non-pregnant individuals, modified and often intensified by pregnancy.

(4) Increase in blood pressure is especially important when it appears in children and young adults. In such subjects there is less apt to be serious damage to vital structures, and hence more permanent benefit can be produced if the cause of hypertension can be removed. The following conditions are especially likely causes of hypertension occurring under the age of 30: psychoneurosis; injury to the brain stem from diphtheria, poliomyelitis or encephalitis; tumors of the adrenals, medullary or cortical; acute and chronic glomerular nephritis; pregnancy, ureteral stricture and pyelonephritis; conditions causing urinary tract obstruction; pyelitis and pyelonephritis; Wilms tumor of the kidney and coarctation of the aorta. In young hypertensive subjects these conditions should be looked for and an especially careful search should be made for masked infections in the kidney, for urinary tract obstruction and for tumors of the kidney or adrenal glands, because these conditions are particularly amenable to therapy.

(5) Is malignant hypertension a disease entity? Our observations, while not entirely conclusive, suggest a negative answer to this question. Of the 100 patients with increased blood pressure nine had typical malignant hypertension. Two of these, both males, were classified as belonging to the stress and strain group because their hypertension was known to have developed during prolonged and severe business stress associated with unusually hard mental work. Three patients, all females, with typical malignant hypertension, had pyelitis or pyelonephritis, the vascular lesions apparently developing secondarily as the result of hypertension induced by the renal infection. A sixth patient had some of the manifestations of pituitary basophilia, had been under unusually severe business strain and had three positive urine cultures for streptococci. He was classified in the mixed group. In the other three patients with malignant hypertension no apparent etiological factors could be found and the nature of their hypertension was not classified. Until more conclusive evidence is available it seems best not to consider malignant hypertension as an etiological entity. Apparently, it represents a severe reaction in the renal arterioles to increase in blood

pressure. Presumably the stimulus responsible for hypertension causes unusually marked vasoconstriction in the afferent glomerular vessels of some especially predisposed young subjects. Such vasoconstriction apparently leads to injury to the vessel wall with narrowing of the lumen. The renal ischemia so induced causes further hypertension, which in turn aggravates the renal vasospasm. The progressive vicious cycle so brought about seems to be responsible for the clinical picture designated as malignant hypertension. Such a concept accounts for the rapid appearance of malignant hypertension in persons who have previously had the picture of benign hypertension. If it be assumed that malignant hypertension is an entity, instances of this type have to be ascribed to coincidence of two different diseases, both of which can elevate the blood pressure.

The purpose of this communication has been to point out that a considerable body of knowledge is available concerning the conditions responsible for hypertension. Even though this knowledge is as yet far from complete, that portion of it which is at hand can be utilized. The underlying factors responsible for increase in blood pressure can be determined in some cases and important aggravating factors can be found in the great majority of cases. By recognizing and treating such factors much can be accomplished in the alleviation of that important group of disorders which are characterized by hypertension

SUMMARY

A study has been made of 100 patients with increase in blood pressure in an attempt to classify them according to conditions playing a rôle in the production of the hypertension. Although it has not been possible to distinguish with certainty between underlying and aggravating causes of hypertension, and although in many of the patients more than one factor has seemed to be of importance, most of the individuals have displayed one major condition which appeared to be the most significant cause of the rise in blood pressure. The patients have been classified as follows:

(1) *Neurogenic Group* (16 cases). This included six psychoneurotic subjects, five other patients who were living under unusually severe conditions of mental stress when the hypertension appeared, two patients in which the hypertension disappeared permanently after coronary thrombosis and in whom it is thought that the increase in blood pressure may have been of reflex origin from the heart, two patients with acute diseases involving the brain stem and one subject with increased intracranial pressure as the result of skull fracture.

(2) *Endocrine Group* (20 cases). This included 10 subjects presenting evidence of basophilic hyperplasia of the pituitary gland, and 10 women in whom the onset of hypertension coincided with the menopause.

(3) *Metabolic Group* (10 cases). This included seven patients with hypercholesterolemia who were suspected of having atheroma of the large

renal vessels and three patients with increased blood uric acid. In the latter subjects urate deposits in the kidneys were thought of as possible causes of the hypertension.

(4) *Renal Group* (30 cases). This included eight subjects with obstruction to the urinary tract, eight patients with a history of stone, colic or hematuria, one patient with coarctation of the aorta, five patients with a history of pyelitis and eight subjects with evidence of masked pyelonephritis. In the two latter sub-groups evidence of renal infection was often minimal and was obtained only by unusually thorough examination.

(5) *Heart Failure Group* (2 cases). Both of these individuals had hypertension during congestive heart failure, the blood pressure returning to normal and remaining at a relatively normal level following improvement in the cardiac condition.

(6) *Mixed Group* (5 patients). These individuals had evidence of more than one of the conditions which have already been mentioned, no single factor seeming to be more important than the others.

(7) *Unclassified Group* (17 cases). In these subjects no definite condition which might have been responsible for the increase in blood pressure could be determined.

It has been pointed out that whereas in some of these groups no effective therapy is available, in other groups the conditions which are apparently responsible for the increase in blood pressure can be markedly benefited provided that such conditions are recognized by careful studies of the individual patient.

CASE REPORTS

Case 1. P. G., a 27-year old white male, became ill nine months before admission, following the death of his father from angina pectoris. He developed a marked cardiac neurosis with hypertension and tachycardia. History otherwise was negative. The only positive physical finding was a blood pressure of 186/106. Laboratory findings were all negative. Under evipal anesthesia the blood pressure declined to 130/80 and then returned to the previous level. There was no significant fall in pressure during a six-week period of bed rest in the hospital. The blood pressure decreased to normal levels after psychotherapy and has not been recorded above 140/80 during the year following admission.

Case 2. C. F. N., a 57-year old white male, had had his blood pressure taken frequently during yearly physical examinations. In 1933 he had difficulties in his business and in addition to working for long hours under severe mental stress, finally lost his business to the bank. At this time he began to have severe headaches and his blood pressure which had previously been normal was found to be elevated. Subsequently, he had a typical attack of hypertensive encephalopathy. He became very depressed and anxious about himself. He then obtained a position which gave him reasonable economic security but allowed him to lead a restricted life. The blood pressure declined rapidly from the previous systolic level of 220 to 160-180.

On admission to the hospital the blood pressure was 180/100. Following reassurance, mild sedation and 24 hours rest in bed it declined to 124/80. After resuming his usual activities he remained free of symptoms for several weeks. The subsequent course is unknown.

Case 3. A. J., a 66-year old white male, who had been under observation for several years, had always had a normal blood pressure until he developed angina pectoris. For several months, during which he was having frequent attacks of pain, the blood pressure ranged from 190/120 to 172/100. He then had coronary thrombosis with marked circulatory collapse and was almost moribund for several days. During the 18 months since recovery the blood pressure has been taken on numerous occasions and has usually been 120-130/80-95. The highest pressure observed since coronary thrombosis was 150/100. He remains free of angina pectoris and has no symptoms of diminished cardiac reserve.

Case 4. W. G., a 20-year old boy, entered the hospital with acute anterior poliomyelitis of the spinal cord and brain stem. History and examination were negative except for signs of poliomyelitis and hypertension (200/92). Postmortem examination confirmed the diagnosis of poliomyelitis and was otherwise negative.

Case 5. S. C., an 8-year old girl, entered the hospital with tonsillar and pharyngeal diphtheria. The blood pressure on admission was 120/80. As the acute symptoms and fever subsided she developed cranial nerve palsies. Associated with this her blood pressure rose gradually to 190/138 and then as signs of paralysis cleared returned to a normal level—110/70—where it has remained. The urine was at all times essentially negative.

Case 6. A. N., a 40-year old white female, was first seen with post-diphtheritic paralysis and bulbar symptoms. Her blood pressure at this time was 150/110. The urine was negative at this time. As the bulbar symptoms cleared the blood pressure decreased to normal and remained so for about a year, when she began to have some back pain and intermittent chilly sensations. At this time her urine contained abundant pus and her blood pressure remains elevated.

Case 7. E. H., a white female, aged 37, complained of headaches and weakness. These symptoms had been present for two years during which time menstruation had been irregular and scanty. Both parents had died of hypertension. She was 63 inches tall and weighed 191 pounds. The obesity involved the arms and thighs somewhat but was mainly confined to the trunk, especially the abdomen. The neck was quite short, the complexion was ruddy, the blood pressure varied between 180-200/105-110. There were a few plum colored striae over the abdomen. The fasting blood sugar was normal but there was an abnormally pronounced and prolonged rise in the blood sugar curve following the administration of glucose. Following a course of deep roentgen-ray therapy over the pituitary gland the subjective manifestations disappeared and the blood pressure gradually declined to 130/70. During the next three months the blood pressure was measured repeatedly and the highest value found was 150/90.

Case 8. E. G. was a 47-year old white male who had many complaints. He was found to have myxedema, peripheral neuritis due to vitamin B₁ deficiency and severe hypertension. He had a history of having passed bloody urine on several occasions. There was no history of urinary tract infection. On examination his urine was at times negative and at times showed albumin, red cells and casts. The blood pressure was 230/140. The blood cholesterol was 333. He developed a dissecting aneurysm of the aorta and died. At autopsy the kidneys showed many old healed infarcts, marked large vessel arteriosclerosis and moderate arteriolar sclerosis.

Case 9. L. B., a 72-year old negro male, was first seen in 1933 with an enlarged prostate and a blood pressure of 140/90. Prostatectomy was done and a microscopic diagnosis of adenocarcinoma made. He developed *B. coli* urinary tract infection. The blood pressure gradually rose during the following years and from 1935 until readmission to the hospital ranged between 180/110 and 230/130. When examined in the hospital the findings were those of a chronic cystitis and pyelonephritis with a *B. coli* infection. He was treated with sulfanilamide. The urine cleared up in nine days. His blood pressure remained up during his stay in the hospital but two

weeks after discharge it was 130/90, and the following week and for two months since then has remained within normal limits.

Case 10. M. F. J., a 45-year old Negress, has been followed for 10 years because of chronic heart failure due to rheumatic heart disease with mitral stenosis and insufficiency. Gradually during the last eight years she has developed increase in blood pressure. During this time she has had a markedly enlarged uterus due to myoma. She has had no urinary symptoms. The urine contained varying amounts of albumin, a few white cells and occasional casts. Urine cultures were positive for *B. coli*. At autopsy the left kidney was markedly contracted and displayed the typical changes of advanced pyelonephritis with dilatation of the ureter secondary to pressure from the myoma. The right kidney was normal except for early granular changes in the cortex and slight changes in the vessels.

Case 11. C. S., a 34-year old white female, was first seen in 1931. She had a history of pyelitis appearing during pregnancy seven years previously. Since that time there had been occasional attacks of frequency and burning and she had been treated by a urologist for cystitis and pyelitis. The blood pressure in 1931 was 160/100. The urine showed a trace of albumin and there were 10-15 white blood cells per high powered field in the centrifuged specimen. She was not seen again until 1938. During the interval she had continued to have occasional attacks of frequency and burning on urination but these symptoms had not been pronounced. Examination in 1938 revealed marked contraction of the retinal arteries and early papilledema. The blood pressure was 264/148, and there was well marked cardiac hypertrophy. Intravenous and retrograde pyelograms showed dilatation of the left ureter and of the pelvis of the left kidney. The urine contained a moderate amount of albumin but only rare white blood cells. However, specimens obtained from the two kidneys by ureteral catheter each showed a few clumps of white blood cells and numerous gram negative bacilli. Repeated urine cultures were positive for colon bacilli.

Case 12. M. L., a 25-year old Negress, was first found to have elevated blood pressure in 1934 during a routine examination. For several years she had noted mild back pain associated with fatigue. When seen in 1939 she was four months pregnant and the blood pressure was 175/110, the examination being otherwise negative. The catheterized urine showed a few red blood cells, very rare clumps of white blood cells and streptococci. Cultures showed streptococci. Pyelograms revealed slight bilateral dilatation. During three weeks in the hospital her blood pressure averaged 160/120. She was treated with sulfanilamide. The infection was cleared up and her pressure subsequently dropped to normal where it has remained throughout her pregnancy and for four months since delivery.

Case 13. S. L., a 33-year old white female, complained of blurring and loss of vision and some urinary symptoms which consisted of periods of burning and frequency. During such periods she had at times slight facial edema. She was admitted to the hospital and was suspected of having a brain tumor because of marked choking of the discs. An exploratory craniotomy was done. This was negative. The urine was negative except for a few white blood cells. Culture showed streptococci on many occasions. After a period of three weeks in the hospital, during which time the blood pressure averaged about 170/120, she was treated with sulfanilamide. The infection subsided, the blood pressure dropping to normal, where it remained the following year.

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V. CUTANEOUS XANTHOMATOSIS *

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THE purpose of this paper is to present a working classification of cutaneous xanthomas,^{1, 2, 3} with brief mention of their distinguishing features, and to report a case of extensive xanthoma tuberosum in which no evidence of systemic disease could be demonstrated despite a very marked increase in the blood and tissue lipoids.

TYPES OF CUTANEOUS XANTHOMATOSIS WITH DISTINGUISHING FEATURES

1. *Nevoxantho-endothelioma* (McDonagh):

- Onset early in life. Groups of papules or nodules on extensor surfaces.
- Spontaneous involution.
- Normal blood lipoids.
- Characteristic histopathologic picture, including endothelial, as well as Touton, giant cells.

2. *Juvenile xanthoma*:

- Usually presents characteristics of type 3 (below), occasionally of type 4.
- Rarely presents characteristics of a combination of types 3 and 4, with or without evidence of Hand-Schüller-Christian disease.
- Hereditary tendency.
- Frequent occurrence of severe cardiovascular disease, rarely of hepatosplenomegaly, with features of both types 3 and 4.

3. *Xanthoma tuberosum* (the most common type):⁵

- Nodules, papules, or plaques predominating on extensor surfaces, including tendon sheaths.
- Definite hyperlipemia.
- Usually an increase in cholesterol in both blood and cutaneous lesions.
- Frequent association of severe cardiovascular disease, especially angina pectoris and intermittent claudication.
- Involution of lesions frequently follows low-fat diet.†

* Submitted for publication July 25, 1938.

† Thannhauser and Magendanz referred to xanthomatosis of the central nervous system described by van Bogaert and others in association with xanthoma of the tendons and xanthoma tuberosum. So-called extracellular cholesterosis of Urbach can also, I believe, be regarded as a variant of xanthoma tuberosum.^{1, 4}

4. *Xanthoma disseminatum*:

Fine papules and plaques predominating on flexural surfaces, especially axillary folds, and also mucous membranes, including pharynx and larynx.

Frequent involvement of pituitary region and associated mild diabetes insipidus.

Normal blood lipoids.

Tissue lipoids as in type 3.

No response to any diet or other type of treatment.

5. *Xanthelasma of eyelids*:

May be seen in any type of xanthoma, especially types 3 and 4.

Moderate elevation of blood lipoids occurs in 70 per cent of cases of xanthoma limited to eyelids alone.

Often associated with severe cardiovascular disease.

Histopathologic picture is typical for xanthoma.

6. *Xanthoma diabeticorum*:

Multiple discrete to confluent papules predominating on extensor surfaces with predilection for palms and soles.

Usually a severe diabetes with marked lipemia and prompt involution under diet and insulin.

Involuting lesions reveal extracellular as well as intracellular deposits of lipoids outlining the reticulo-endothelial system.

7. *Necrobiosis lipoidica diabeticorum*:

Varying sized plaques, chiefly on extremities; may follow trauma.

Usually associated with diabetes.

Normal blood lipoids.

Characteristic histopathologic picture with central necrosis and extracellular deposits of lipoids usually with an excess of free cholesterol in the tissues.

8. *Lipoid proteinose (Urbach)*:

Hereditary tendency.

Nodular, hyperkeratotic, verrucous and sclerosing lesions predominating on face, extremities, and mucous membranes, including larynx.

Histochemical evidence points to disturbance in phosphatides with extracellular deposits of lipoids about blood vessels.

9. *Xanthoma in relation to disease of the liver*:

Usually type 3, occasionally a combination of types 3 and 4, or type 4 alone in terminal stages.

Lesions on palms predominate.

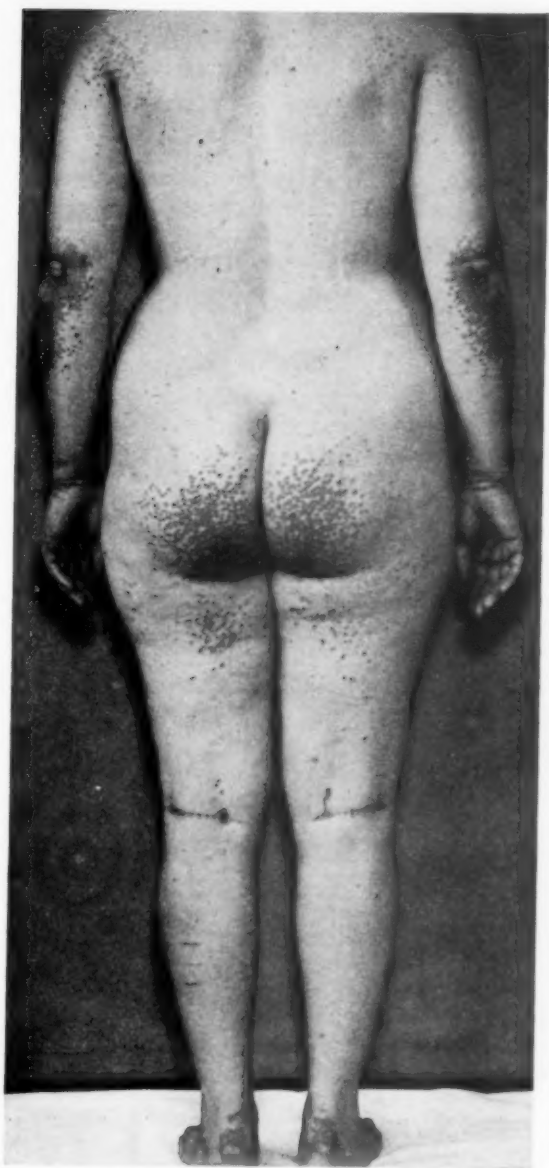


FIG. 1. Xanthoma tuberosum, involving extensor surfaces and also occurring in creases and folds of skin or in areas subject to friction.

Cutaneous xanthomas are usually secondary to hepatic involvement but may be primary.

Hyperlipemia without relative increase in free cholesterol is the rule. Secondary xanthomatosis following obstructive jaundice associated with stricture of the common duct is the most common type;

also hepatosplenomegaly with cutaneous and mucous membrane lesions with or without jaundice and marked increase in phosphatides and free cholesterol in the blood and tissues.

10. *Xanthoma in relation to tumors:*

- a. So-called "xanthic tumors" of the tendon sheaths independent or associated with type 3. These are not malignant lesions. Hyperlipemia
- b. Histiocytoma (dermatofibroma). Usually a hyperlipemia.
- c. Xanthic changes in true malignant neoplasms. Distinguished by concomitant histopathologic findings.

CASE REPORT

A woman, aged 28 years, was examined at the Mayo Clinic in July, 1937, because of cutaneous lesions of six years' duration. These started as macular areas on both palms; nodules and papules then appeared on the extensor surfaces about the elbows, knees, Achilles tendon, heels, and hips. The lesions also appeared on the flexural

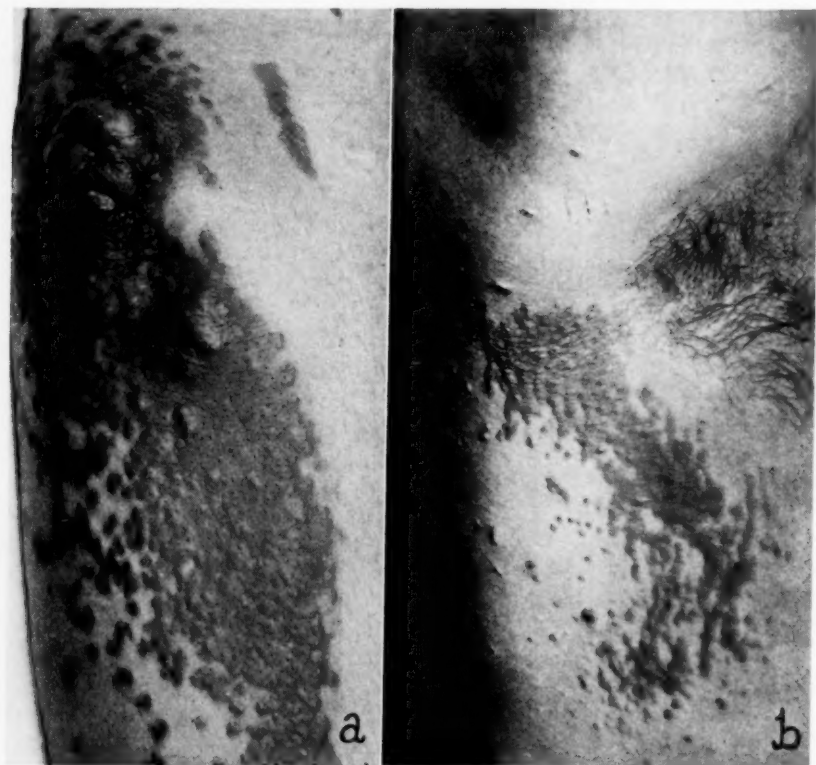


FIG. 2. Xanthoma tuberosum, showing *a*, xanthomas of various sizes and xanthomatous plaque on elbow, and *b*, xanthomas at margins of axilla. The deep axilla is not involved as is the case in xanthoma disseminatum.

surfaces of the elbows, axilla, wrists, and across the foot and groin. No history could be obtained of diabetes or diabetes insipidus, or of cardiorenal, hepatic, or other systemic disease. The family history was negative.

The nature of the lesions is shown in figures 1 and 2. It will be noted that where the lesions occurred on the flexural surfaces, they were in the creases or folds of the skin; elsewhere they occurred where there was friction from clothing. There was no involvement deep in the axilla. The lesions varied from a light yellow to reddish-brown; the older and larger lesions were of a deeper or brownish hue. General examination gave essentially negative results, including roentgenograms of the legs for occlusive arterial disease, and roentgenograms of the pituitary gland, sella turcica, and of the thorax. Electrocardiograms were essentially normal. There was no involvement of the mucous membranes of the mouth, larynx, or pharynx, or of the eyelids. The patient was somewhat obese, her height being 60 inches (152 cm.) and her weight 167 pounds (75.7 kg.). The liver could not be palpated. A liver function

TABLE I
Biochemical Studies of Blood and Tissue

Biochemical studies	Blood		Tissue	
	9-9-37		7-12-37	
	Mg. per 100 c.c. plasma	Per cent of total lipoids	Per cent of wet weight	Per cent of total lipoids
Total cholesterol	667	39	5.5	63
Cholesterol esters	417	62*	2.5	45*
Lecithin	594	34†	2.0	24†
Fatty acids	1056	61	3.27	37
Total lipoids	1723		8.7	

* Per cent of total cholesterol.

† As per cent of total lipoids.

test revealed no retention of dye. The blood and tissue lipoids are given in table 1. A specimen for biopsy from early and late lesions revealed a typical picture of xanthoma with, however, a considerable amount of fibrosis.**

COMMENT

The onset of the xanthoma in this case was too late in life to class it as being of the juvenile type. The variation in color and size of the individual lesions was well shown, and also the fact that solid plaques sometimes occur in the tuberosae as well as in the disseminate forms of xanthoma. The lack of involvement of the mucous membranes or deeper portions of the axilla, the predominance of lesions on the extensor rather than on the flexural surfaces, together with the marked lipemia, ruled out xanthoma disseminatum. The involvement of the palms suggested the possibility of a diabetes or

** After this paper was submitted, the patient returned to the Mayo Clinic in August, 1938. There had been no change in the cutaneous lesions and the value for blood lipoids was practically the same. The patient had failed to follow an animal-fat-free diet. There was still no evidence to be found of systemic involvement of any type.

hepatic disease, but this could not be demonstrated. The increase in free cholesterol, as contrasted with combined cholesterol, in the tissues is probably best explained on the basis that the lesion chosen for analysis was an old one, revealing histologically, a great deal of fibrosis and a great deal of extracellular deposits of lipoids. As a result of my own experience and on reviewing the literature it seems that when, histologically, many of the lipoids are to be found extracellularly, there is likely to be either an excess of free over combined cholesterol or an increase in lecithin.⁴

This case therefore illustrates that a disturbance in the cholesterol-cholesterol ester ratio does not necessarily imply hepatic disease. We must regard it as an atypical but extensive case of xanthoma tuberosum, uncomplicated at the present time by any demonstrable involvement of the internal organs. Classification of various types of cutaneous xanthoma is important from the standpoint of prognosis and treatment, and also in regard to the type and location of the systemic involvement.

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THE MECHANISM OF THE PSYCHONEUROSES *

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IN the more recent classifications of the psychoneuroses there is a marked trend towards simplification. An attempt is made to class the psychoneuroses as prepsychotic anxiety states. While we are frequently forced to recognize this in our statistical records, there are many cases in which the clinical syndrome does not justify such a classification. The classification which is considered in this discussion is that adopted by the Committee on Statistics of the American Psychiatric Association, and the National Committee for Mental Hygiene in 1934. Accordingly, under this heading are placed disorders of psychogenic origin, or without clearly defined tangible cause or structural change.

PSYCHONEUROSES

1. Hysteria (anxiety hysteria, conversion hysteria).
2. Psychasthenia, or compulsive states.
3. Neurasthenia.
4. Hypochondriasis.
5. Reactive depression.
6. Anxiety states.
7. Mixed psychoneurosis.

The conception of anxiety hysteria¹ is extremely variable. According to one viewpoint, anxiety hysteria is conversion hysteria accompanied by anxiety. Another method of classification includes under anxiety hysteria those reactions which are presented under the head of psychasthenia.² From still another viewpoint anxiety hysteria should be classified with the anxiety states.

Patients who present conversion symptoms or phobias, but who are relatively free from recurring attacks of anxiety are usually grouped under conversion hysteria or psychasthenia, although the cases showing predominantly obsessions, compulsive tics and spasms and phobias are preferably classified as psychasthenia. Because of the frequent combination of psychoneurotic symptoms in individual cases the classification of mixed psychoneurosis may be proper in many instances.

It appears therefore that hysteria is not a desirable designation, and is not an entity. The same is true of psychasthenia or compulsive states² and hypochondriasis,⁴ the latter occurring not infrequently in the major psychoses. A statistical record shows that 65 per cent of the cases diagnosed

* Received for publication February 25, 1938.

hysteria during a period of 10 years were later hospitalized, and classified as schizophrenia.

A very different type of disturbance, and with a more constant clinical picture, is neurasthenia,³ and while neurasthenia is regarded as an entity without an organic basis, there is undoubtedly a physiological dysfunction as the basic cause. The motor and mental fatigability, diminished power of concentration, low blood pressure and other inefficiencies are not without cause. This clinical picture is a marked contrast to the conditions previously described.

The reactive depressions,⁵ which show depression in reaction to obvious external causes that might naturally produce sadness, such as bereavement, sickness and financial and other worries, are in proportion to cause and effect when we consider the constitutional instability of the individuals so afflicted.

The anxiety states,⁶ presenting more or less continuous anxiety and apprehensive expectation, with paroxysmal exacerbations, associated with physiological signs of fear, precordial distress, palpitation, dyspnea, nausea, gastrointestinal distress, diarrhea, emotional tension, irritability and intense self-preoccupation, present physical manifestations sufficient to be regarded as causative factors.

Such is the psychopathological aspect of the psychoneuroses.

However, whether or not our present understanding of the psychoneuroses qualifies us to speak of them as pathological units, our working hypothesis will be more fruitful if we postulate that there are such units, provided that we realize our classification is a mere scaffolding, to be discarded without emotion or egoism when a more solid structure appears. Our understanding of certain of the psychneuroses has reached the point where etiology, clinical syndrome, diagnostic criteria and pathology are recognizable.

The regularity with which certain psychneuroses occur in the same body types and the regularity with which other physical signs appear, strengthen the theory that the entire range of mental disorders, including the psychoneuroses, has a somatic basis intimately related to glandular balance, and since there are constitutional types conveniently summarized in the physique, so also are there temperamental types for which the word *psychique* is available.

The asthenic or asthenic-athletic physique is more often of the schizophrenic reaction *psychique*, as in hysteria, psychasthenia and hypochondriasis, while the pyknic habitus and the cycloid temperament are the rule as in neurasthenia, reactive depression and anxiety states. Furthermore, there are more or less constant physical manifestations intimately associated with the asthenic and asthenic-athletic physique and the schizoid *psychique* which differ materially from those observed in the pyknic habitus and the cycloid temperament.

It was possible to classify 400 cases of psychoneuroses into the following two groups on a somatic basis:

Hysteria A. Psychasthenia Hypochondriasis	{ Asthenic and asthenic-athletic habitus. Spasm of the radial arteries. Acrocyanosis. Dermographia. Segmental hypothermia. Excessive sweating and saliva.
Neurasthenia B. Reaction depression Anxiety states	{ Pyknic habitus. Small pulse volume, low blood pressure. Pale skin. Segmental hyperthermia. Anorexia, gastrointestinal and genitourinary disorders.

It is in group B that we frequently find gastrointestinal disturbance, changes in tonus of the stomach and bowel, in the secretions, and change in the tonus of the genitourinary apparatus, while in group A disturbances of the peripheral circulation are more common; vessel spasm, cyanosis, etc. I fully realize that the emotions play an important part in the circulatory disturbance; on the other hand endocrine imbalance is an important factor in depressions, exaltations, fear and anger.

The dermatologist recognizes the influence of increased excitability and emotionality in certain skin conditions, and speaks of dermothalassia in compulsion neuroses, and of emotional urticaria, hysterical pemphigus, abnormal hair growth, anomalies of sweat and of the nails.¹

In these physical manifestations we recognize a disturbed mechanism of the human organism, intimately connected with the vegetative nervous system, and with a reciprocal relationship with the glands of internal secretion.

Associated with the physical manifestations there is a more or less constant psychic syndrome characteristic of each group. In group A the most constant mental characteristics are: Lack of attention, depression of spirits, loss of self-control, excitement without apparent cause, uncontrollable emotional outbursts, laughing or weeping, insidious loss of power of decision, and unwillingness to assume responsibility.

In group B the most apparent and constant psychic syndrome is that of sadness, fear, anxiety and hopelessness, with mild agitation, intense self-preoccupation, and inadequacy.

We realize therefore, that there can be disturbance of the function of the central nervous system as the result of abnormal working of either the endocrine mechanism or of the parasympathetic and sympathetic nervous systems; just as there might be impaired activity of the glands of internal

secretion or of the vegetative nerves secondary to deranged function of the central nervous system. We also recognize that the manifestations in the psychoneuroses may be the result of abnormal function of other bodily organs, and of general toxic or infectious processes which indirectly affect the nervous system. A peripheral vasospasm may also mean a cerebral vasospasm, while a secondary anoxemia, or a toxic state, bacterial or chemical, may bring the same result.

If we apply the theory that a balance exists between the activities of the sympathetic and the parasympathetic division so that visceral function is resultant of the balance of these two forces, and translate the anatomic units of this conception into chemical terms, the activity of any organ involved by autonomic stimulation is the result of a balanced activity between acetylcholine, which is produced by the *parasympathetic nervous system*, and the more hypothetic series of chemical substances produced by the *sympathetic nervous system* at the neurovisceral junction, which are called sympathin E. and I. These are like adrenin, so the chemical concept of balance may be stated as the result of the effects of cholinergic and adrenergic substances. To this concept has been added the hypothesis of the activity of the esterases, substances produced either by the reacting cell or by the tissues in general. These substances (choline-esterase) are believed to destroy acetylcholine, and consequently the action of the parasympathetic nervous system is intermittent. The antagonist which acts on sympathin in a similar manner has not been isolated.

Experimental evidence shows that while some functions of an organ are apparently autonomically balanced, there are other functions in the same organs which respond to only one type of drug, and consequently are either cholinergic or adrenergic. The sweat glands are cholinergic; they respond only to chemicals of the acetylcholine group and not at all to the chemicals of the adrenergic type, although they are innervated only by the sympathetic system, and would be expected to react to adrenergic chemicals.²

According to this theory the normal activities of the sympathetic and the parasympathetic division of the autonomic nervous system are dependent upon a balance between two forces. A disturbance of this equilibrium will interrupt the normal activity of any organ involved by autonomic stimulation, resulting in physical manifestations which may be perceived subjectively or objectively.

The results of research which began in 1928 gave us a more tenable concept of many of the physical and also of some of the mental manifestations of the psychoneuroses.

The cases were selected according to body types, physical signs and mental manifestations, as indicated in groups A and B, and 200 cases of each group were treated. The patients in group A were below the age of 30 years, and those in group B under 35 years. The youngest patient was 12 years old.

1. The experimental results with a mixture of CO_2 (20 per cent), and O_2 (80 per cent) in group A were rather striking, and all out of proportion to what one might expect with psychotherapy alone. I am fully aware that this type of treatment may be regarded as psychotherapy, but the patients were immediately relieved of the physical as well as of the mental manifestations. They expressed a feeling of well-being. The objective physical reaction occurred in the following order: General flushing and warming of the skin, muscular hypertonus, relaxation of all muscles and moisture of the skin. However, this treatment does not bring permanent relief, and within 24 hours all of the physical and mental signs recur. Repeated applications give the same results.

The mechanism of the action of CO_2 and O_2 is that the CO_2 is a vasodilator and cholinergic in function, while O_2 increases the blood flow to the brain. This has been definitely proved by animal experiments.³ This reaction results in a fixation of oxygen by the cell dependent upon the acquisition of free oxygen from without.

The application of this experiment in types listed under B gave unsatisfactory results. No change in the physical signs or mental manifestations was noted after the treatment.

2. A much more permanent result was obtained by oral administration of hyoscin hydrobromide ($\text{C}_{17}\text{H}_{21}\text{O}_4\text{NHBR}$) over a longer period of time. To avoid any physiological disturbance such as dryness of the mouth and throat, dilation of the pupils, etc., the drug was given in small doses, gradually increased from 1/300 grain to 1/75 grain. The dose is increased at intervals of eight days until the maximum dose is reached. In this manner all patients acquired a tolerance without any physiological disturbance.

The physical signs and mental manifestations gradually disappeared giving a more or less permanent result. Hyoscin hydrobromide is a vasodilator, slows the pulse rate, raises the pulse volume and increases the blood flow to the brain.

The application of this drug in group B was unsatisfactory.

It appears, therefore, that $\text{CO}_2\text{-O}_2$ and hyoscin hydrobromide are cholinergic in function.

3. Benzedrine sulfate (benzyl-methyl carbamine) was used as an adrenergic drug in both groups with unsatisfactory results with group A. Much more gratifying were the results with group B, especially in those cases where mental depression was a prominent sign, and gastrointestinal and genitourinary hypertonus existed.

Benzedrine sulfate increases the blood pressure and relaxed spasm of the gastrointestinal tract and relieves bladder hypertonus of the functional or organic type.

Ephedrine and epinephrine are adrenergic drugs. The results with these drugs were not definite in group A. Ephedrine was the most satisfactory in group B. Many cases found in group B were decidedly benefited

by digifolin (representing digitalin and digitoxin). Coramine (pyridine-B carboxylic acid diethylamide) gave good results in relieving the mental depression in the reaction depressions and the anxiety states.

In many of these cases with low blood pressure, small pulse volume, pale skin, the mental manifestations are apparently dependent upon a cerebral anoxemia. Since the arterial blood supply is dependent upon systemic pressure, any of the factors known to reduce arterial pressure, such as reduced systolic discharge, the result of myocardial inefficiency, decreased conductivity of the bundle of His, lowered peripheral resistance and decreased heart rate reduce venous return, diminishing the cerebral blood flow to a degree lower than is necessary to maintain cerebral function with a consequent anoxemia, and since the adrenergic drugs and those drugs which increase the myocardial force are beneficial, it would appear that a cerebral anoxemia exists.

The case histories related below are representative of patients selected for this work. Only positive findings are recorded.

CASE REPORTS

Case 1. White male, aged 19, asthenic body type. Complained of numbness of the legs, coldness of the hands and feet, anxiety attacks with palpitation of the heart, and shortness of breath. Lacks ambition, and has difficulty in applying himself. This condition came on at the age of 14, and has been more or less continuous.

He has had no other serious illness, and no injury. Tonsillectomy and adenoidectomy were performed at the age of 10 years.

The patient is the second child of a family of four, and has two brothers and one sister, all well and normally active. The father is 50 years old, emotionally stable, and a man of good habits. The mother is of nervous temperament, aged 43.

The examination revealed asthenic habitus, weight 149 pounds, height 72½ inches. Spasm of the radial arteries, acrocyanosis, pulse 84. B.P. 140 mm. of mercury systolic and 80 diastolic. Cold hands and feet, wet palms and soles. Mild anxiety, over-apprehensiveness and a feeling of insecurity.

Hyoscin hydrobromide was administered orally according to the method described above. In five weeks the patient was entirely free from the symptoms described.

Case 2. A white female, aged 16. Asthenic habitus. Complained of attacks in which she feels like falling. This occurs sometimes when she is sitting down or standing erect. Sometimes she awakens in the night calling out that she is falling. She has no recollection of this the following morning. She also has frontal headache and pain in the eyes. She stated that she is easily frightened. The first attack came on at the age of 14 years. Since then the attacks have been recurring at two or three day intervals.

She has had no serious illness. Fracture of the wrist and injury to the knee occurred from a fall; good recovery. Tonsillectomy at 11 years.

The patient lives on a farm, attends the community school, and is in the ninth grade. Her scholastic record is good.

The father is 50 years of age. He is irritable and nervous. The mother is well, even-tempered and cheerful. There are four brothers, all well, and two sisters, both well.

The examination showed a well nourished young girl without physical deviations, weighing 110 pounds; 5 feet 5 inches in height. B.P. 120 systolic and 70 diastolic.

Spasm of the radial arteries. Pulse 64 per minute. The hands and feet are cyanosed. Palms and soles wet; marked dermatographia. She was in a cheerful mood, with good contact and normal behavior.

Histamine was given orally for a four week period, with temporary relief. Hyoscin hydrobromide relieved her condition.

Case 3. White male, aged 32, pyknic habitus. Became mildly depressed and withdrew from all social activities. He feared that he had cancer of the gastrointestinal tract. He complained of general weakness, gastrointestinal distress, gaseous distention of the abdomen, eructations, alternating constipation and diarrhea, and enuresis. He was no longer able to apply himself to his occupation as an attorney at law. This difficulty was of about 10 years' standing. Prior to the present illness the patient was in good health, and since his childhood days has had no serious illness or injury.

His childhood days were happy and he has always been fond of out-of-door activities. He graduated from a University law school and practiced law until three years ago. He is single, and has no unusual responsibilities.

The father died of cancer of the duodenum at 62, and one paternal uncle and one aunt died of cancer. Mother is well at 70.

The physical examination revealed moderate distention of the abdomen, spastic radial arteries, cold hands and feet, palms and soles wet. He was extremely over-apprehensive, fearful, restless, and emotionally unstable.

Benzedrine sulfate was administered orally in 10 mg. doses twice daily, which gave him relief from the gastrointestinal distress and the enuresis. He regained his confidence and was able to return to his former occupation within five weeks.

Case 4. A white female, aged 28, pyknic body type, was subject to recurring attacks of mild mental depression, emotional instability and a feeling of inadequacy. She had been obliged to discontinue her occupation as a teacher on several occasions for from three months to a year. These attacks came on when she was 18 years of age. Prior to this time her health was good and she has had no serious illness.

The father and mother were separated and her home life was unhappy. She is single and is active socially.

The physical examination revealed a small pulse volume. B.P. 100 systolic and 65 diastolic. Heart sounds weak and not easily heard; no murmurs, thrills or irregularity. Her general muscular tone was diminished, the grip in both hands was weak.

Adrenal cortex, in increasing doses to tolerance, raised the pulse volume, the blood pressure, relieved the mental depression, and the patient was able to return to her occupation within six weeks.

Case 5. A white female, aged 32, pyknic body type, complained of gastrointestinal distress, irritable bladder, emotional instability, irritability and mental depression. This difficulty was of five years' standing, and the patient had been repeatedly told by physicians that she had a spastic colitis, and she became fearful that she had a serious organic illness from which she would not recover.

Prior to the present illness the patient's general health was good. She had a tonsillectomy at the age of 13, and an appendectomy at 21, with good recovery. The menstrual history is negative.

Her childhood was happy. She has always been active, and normally of cheerful disposition until she became ill, when a marked change in personality was noted. She was married at 30, and was happy in her family life. Before her marriage she was a teacher. Her father died of uremia at 80. Mother is living and well at 82. One sister died after an illness of eight years, cause not known.

The patient is well developed. Skin pale, muscles well developed, muscle tone diminished. Pulse, small volume, regular, 64 per minute. B.P. 96 systolic and 70 diastolic. Otherwise the physical and neurological examinations were negative.

The patient was talkative, she stressed the topic of colitis and the suffering caused by it. She was in a depressed mood, had frequent crying spells, and a hopeless outlook. She was well oriented and her memory was good. Her attention was variable. Her replies to questions were prompt, coherent and relevant.

Digifoline was given orally in increasing doses, from 10-15 minims three times daily. The patient made a good recovery.

SUMMARY

1. Four hundred cases were selected for this study.
2. It was possible to group 200 cases of hysteria, psychasthenia and hypochondriases according to body type, physical signs and mental manifestations, under one head (A), and 200 cases of neurasthenia, reaction depression and anxiety states, on the same basis, under another head (B).
3. There is a close relationship between the asthenic and asthenic-athletic habitus and hysteria, psychasthenia and hypochondriasis; and between the pyknic habitus and neurasthenia, reaction depression and the anxiety states.
4. The reaction to drugs is antagonistic between the two groups. The conditions grouped under A react favorably to cholinergic drugs, while those in group B are antagonistic to cholinergic drugs but react favorably to adrenergic drugs.
5. Carbon dioxide and oxygen inhalations give relief of the physical and mental manifestations in group A, but give no relief in group B.
6. There is a peripheral vasospasm and increased vascular tension in the psychoneuroses of group A, and diminished peripheral vascular tension in those of group B. If there is also a cerebral arteriolar spasm the result would be a deficient degree of oxygenation and a reduction in the volume of blood referred to the brain or the nervous system as a whole. The same would be true of group B, the result of a peripheral hypotension. The physical and mental manifestations and the drug reactions are in harmony with this view.

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THE PLASMA LIPOIDS IN ARTERIOSCLEROSIS OBLITERANS *

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THE pathogenesis of arteriosclerosis has been the subject of controversy for many years. Among certain investigators there has arisen the concept that the development of atheroma is associated with disturbances of lipid metabolism. The chief reasons for this can be summarized as follows: Pathologists from the time of Virchow⁶ have noted the presence of comparatively large amounts of both cholesterol and neutral fat in atheromatous formations even in their earliest stages of development. More recently Leary^{11,12} has concluded that the development of the entire picture of arteriosclerosis is associated with these lipid deposits and subsequent reaction of the vascular tissue to them. Atherosclerotic lesions can be produced in rabbits by the dietary administration of animal fat or cholesterol, rabbits in these cases developing lipemia and hypercholesterolemia because of their inability to metabolize the animal lipoids satisfactorily. This was first described in 1908, by Ignatowski,⁹ who fed rabbits milk and eggs, and later in 1913 by Anitschkow and Chalatow,¹ who fed them cholesterol. It has been confirmed by Wacker and Hueck,¹⁹ Bailey,² and Leary.¹³ Huber and his co-workers⁸ found that administration of lipocaic to rabbits that were given animal fat prevented the development of the atheroma. Atherosclerosis is commonly seen in association with lipemia in man. In a series of 27 patients who had marked lipemia and hypercholesterolemia associated with xanthoma tuberosum of the skin, Montgomery and Osterberg¹⁵ found a high percentage of coronary sclerosis and arteriosclerosis obliterans of the legs (37 per cent). Necropsy examination in a case of marked lipemia reported by Ochsner and Connor¹⁶ showed an extreme degree of diffuse atherosclerosis. It has been stated by Leary that the incidence of extensive and premature atherosclerosis in diabetic patients was much higher during the period when these patients were fed diets containing large amounts of fat as part of their treatment. This point, however, is somewhat controversial.

Reports concerning the levels of blood lipoids in patients with atherosclerosis in various parts of the body have not been consistent. Mjassnikow¹⁴ found the blood cholesterol usually increased in aortic arteriosclerosis but not increased in a few cases of peripheral arteriosclerosis. Landé and Sperry¹⁰ determined the cholesterol content of serum obtained at necropsy in patients dying accidental deaths who had extensive aortic atherosclerosis and found it no higher than in patients without these lesions. Davis, Stern and Lesnick⁷ found the average free and total cholesterol,

* Read at the New Orleans meeting of the American College of Physicians March 28, 1939.

lipid phosphorus and fatty acids of the blood higher in a group of patients with angina pectoris than in a group of control subjects, although there was considerable overlapping of individual values in the two groups.

Some confusion exists in the literature as to the use of the terms arteriosclerosis and atherosclerosis. Some pathologists have attempted to make a distinction between arteriosclerosis, a degenerative disease of the medial coat of the artery, and atherosclerosis, a disease where the essential change is the development of subendothelial atheroma. A clean-cut differentiation is usually not possible, since the two conditions are usually co-existent. However, their relative proportions may vary greatly.

From the pathologic standpoint arteriosclerosis obliterans of the legs does not differ from occlusive arteriosclerosis or atherosclerosis elsewhere in the body. The lesion consists of three essential components: (1) Degeneration of the medial coat; (2) extensive formation of atheroma, and (3) thrombosis. In the majority of cases the most important component appears to be the atheroma because this forms a considerable portion of the occluding mass and because degeneration of its intimal surface is the main factor in the formation of the thrombus which finally occludes the lumen. In advanced cases the lesions are usually extensive and often associated with considerable atherosclerosis of the abdominal aorta.

This study is based on the determinations of the plasma lipoids in 73 cases of arteriosclerosis obliterans of the legs. These patients did not have diabetes mellitus, as evidenced by normal blood sugar determinations and the absence of glycosuria. Also, they did not have evidence of hyperthyroidism or hypothyroidism. The criteria for making the diagnosis of arteriosclerosis obliterans consisted in definite evidence of occlusion of the major arteries (femoral, popliteal and posterior tibial) of one or both legs, with evidence of arterial insufficiency of the leg muscles or feet, the presence of roentgenographically visible calcification of the arterial walls, the onset of symptoms after the age of 40 years in all cases and after the age of 50 years in 63 of the 73 cases and the absence of a history or findings of superficial thrombophlebitis. In a number of the cases the nature of the lesion was confirmed by pathologic study. The ages of the patients varied from 40 to 79 years.

For comparison the plasma lipoids were studied in a series of 200 individuals of various ages who were considered normal. The criteria for considering these patients normal consisted in the absence of evidence of cardiac or vascular disease, metabolic disorders, diabetes mellitus or dermatoses, as well as the absence of physical findings of any organic disorder.

In both groups determinations were made of the total plasma lipoids and the four fractions, cholesterol, cholesterol esters, phospholipids and fatty acids. The Bloor method^{3, 4, 5} was used for determining the total lipoids and all fractions except the phospholipids, which were determined by the method of Youngburg and Youngburg.²⁰ The blood for the determinations was withdrawn in the morning with the patients fasting. Repeated

determinations on certain of the individuals on different days showed only very small variations in values for the various lipoids from day to day, as has been noted by other investigators.

TABLE I

Concentration of Lipoid Fractions and Total Lipoids in the Plasma of Normal Persons and of Persons Suffering from Arteriosclerosis Obliterans

Control series							
Age	No. cases		Mg. cholesterol per 100 c.c. plasma	Mg. cholesterol esters per 100 c.c. plasma	Mg. phospholipids per 100 c.c. plasma	Mg. fatty acids per 100 c.c. plasma	Mg. total lipoids per 100 c.c. plasma
10-19	3	Mean Range	160 146-187	114 93-137	194 187-208	307 264-330	467 441-517
20-29	66	Mean Range	203 141-309	143 89-241	205 167-278	323 229-484	526 365-753
30-39	53	Mean Range	215 135-292	149 91-214	219 166-278	343 221-492	556 375-769
40-49	41	Mean Range	232 157-370	167 111-309	234 159-316	384 287-651	616 470-919
50-59	25	Mean Range	244 175-354	174 120-268	235 185-309	384 253-579	628 461-827
60-69	11	Mean Range	233 192-303	163 99-214	240 212-315	357 286-492	590 478-784
70-79	1	Mean	172	123	253	393	565
Total	200	Mean Range	218 135-370	154 89-309	220 159-316	350 221-651	568 365-919
Arteriosclerosis obliterans							
40-49	8	Mean Range	290 245-333	208 181-232	266 176-450	454 332-550	744 550-868
50-59	28	Mean Range	275 172-378	194 124-321	284 207-372	431 232-734	706 551-1061
60-69	23	Mean Range	269 214-347	190 152-225	278 203-378	396 249-593	665 487-902
70-89	14	Mean Range	215 139-327	160 88-261	222 120-321	372 225-646	587 404-973
Total	73	Mean Range	263 139-378	186 88-321	267 120-450	411 225-734	674 404-1061

A summary of the results in both groups is given in table 1, which shows mean and range for the various lipoid fractions in each group and in the various age decades of both the series of cases of arteriosclerosis

obliterans and the control series. It should be noted that the age distribution in the two series is not exactly parallel. However, a fairly large series of cases in both the control and the arteriosclerotic groups falls between the ages of 40 and 69 years.

It is noteworthy that the range of values for total lipids and for each fraction is rather great in the control group. This has been noted by other investigators. It is also noteworthy that there is an increase in the mean values in each succeeding decade up to the age of 60 years, after which there is a slight decline. It might be argued that in selecting a group of normal persons for comparison with arteriosclerotic patients only young individuals should be used, as even after the age of 30 years many might have undetectable although well-developed arteriosclerosis of the aorta or other visceral arteries. Equally good arguments can be advanced for comparing only corresponding age groups. However, this point is of more theoretic than practical importance, since either method of selecting the controls leads to essentially the same conclusion.

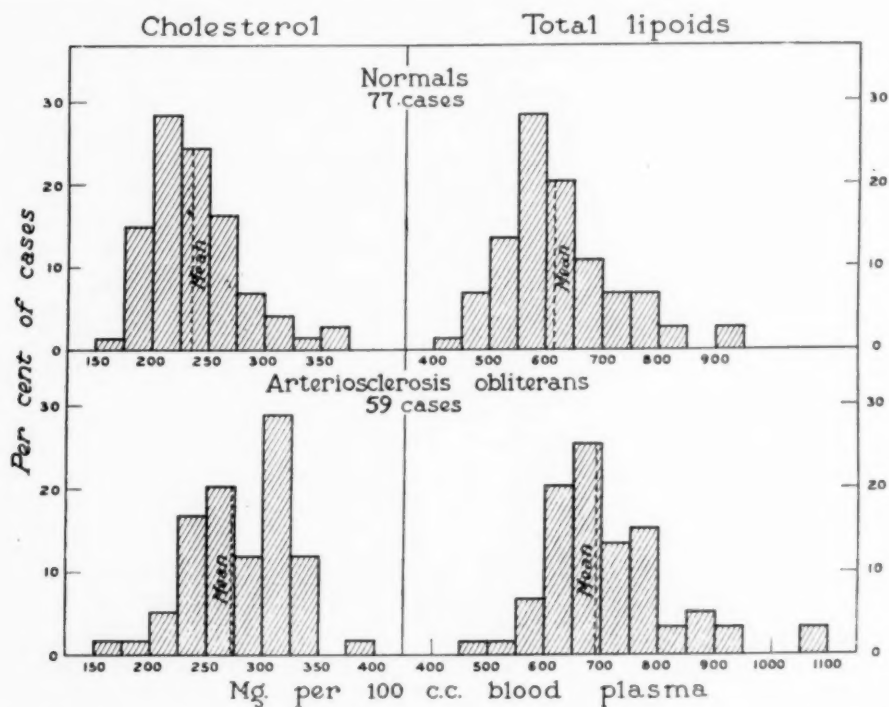


FIG. 1. Frequency distribution of plasma cholesterol and total lipids in the control series and in patients with arteriosclerosis obliterans in the same age groups (40-69 years).

A comparison of the control cases and the cases of arteriosclerosis obliterans with regard to range of the total lipids and various fractions shows very little difference between the two. However, there is a definite differ-

ence in the means, these being consistently greater in the arteriosclerotic group. The same is apparent if one compares only those cases in each group which fall within certain age decades (40-49, 50-59 and 60-69), although the difference is slightly less than it is in a comparison of the entire groups. The difference in mean values is essentially proportional for each of the lipid fractions.

Figure 1 shows the frequency distribution of the plasma cholesterol and total lipoids in the control series and patients with arteriosclerosis obliterans between the ages of 40 and 69 years. There is a considerably larger percentage of higher values in the arteriosclerotic group, particularly of cholesterol higher than 300 mg. per 100 c.c. and total lipoids higher than 700 mg.

In considering the plasma lipid values in the group of arteriosclerotic patients alone it is noteworthy that there is in general a gradual decrease in mean values for each fraction with increasing age and that in the 14 patients between the ages of 70 and 89 years the mean values were approximately the same as the means for the entire normal group (table 1). One possible reason for this is that most of these elderly patients had gangrene, had eaten poorly and had lost weight as the result of persistent pain, loss of sleep and chronic toxemia.

TABLE II

Concentration of Cholesterol and Total Lipoids in the Plasma of Normal Persons, of Persons Suffering from Thrombo-Angiitis Obliterans and of Persons Suffering from Arteriosclerosis Obliterans

		Mg. cholesterol per 100 c.c. plasma	Mg. total lipoids per 100 c.c. plasma
Control group 200 cases	Mean Range	218 135-370	568 365-919
Thrombo-angiitis obliterans (Roth, Maclay and Allen) 36 cases	Mean Range	192 102-273	563 360-871
Arteriosclerosis obliterans 73 cases	Mean Range	263 139-378	674 404-1061

Another comparison is made in table 2, in which mean and range values for plasma cholesterol and total lipoids in the arteriosclerotic and control groups are compared with similar values obtained in a study of patients with thrombo-angiitis obliterans by Roth, Maclay and Allen.¹⁷ The determinations of the blood lipoids in the cases of thrombo-angiitis were done under the same conditions, by the same technicians and in the same laboratory as for the control and arteriosclerotic groups. It will be noted that the mean values in this series of cases of thrombo-angiitis obliterans are actually lower than in the control series and that in none of the cases of thrombo-angiitis did the cholesterol exceed 273 mg. per 100 c.c. of plasma. It seems justified to state, therefore, that in a patient with chronic occlusive arterial

disease of the lower extremities where the exact nature of the lesion is indeterminate by other criteria a plasma cholesterol value of more than 300 mg. per 100 c.c. is definitely supportive evidence for a diagnosis of arteriosclerosis obliterans, and that a plasma lipid value of less than 200 mg. per 100 c.c. is definite, although not certain, evidence in favor of the diagnosis of thrombo-angiitis obliterans.

In a recent publication by Turner and Steiner¹⁸ it was stated that in normal individuals it is not possible to reduce the concentration of the cholesterol in the blood by diet. Eight of the 73 patients with arteriosclerosis obliterans included in this study were given a low fat diet. This consisted of carbohydrate 420 gm., protein 60 gm., and fat 30 gm., of which 15 gm. were animal fat; the diet was supplemented by one capsule of haliver oil a day. This diet was well tolerated by all the patients. In four of the eight no reduction in the plasma lipoids occurred. In the other four definite reduction occurred (table 3). In case 3 pulsations in the

TABLE III
Effect of Low Fat Diet in Arteriosclerosis Obliterans

		Mg. cholesterol per 100 c.c. plasma	Mg. phospho- lipids per 100 c.c. plasma	Mg. total lipoids per 100 c.c. plasma
Case 1	Before diet	287	255	739
	After diet 2 mos.	241	232	572
Case 2	Before diet	321	348	735
	After diet 2 wks.	245	316	635
Case 3	Before diet	260	243	656
	After diet 4 wks.	198	232	570
Case 4	Before diet	252	325	628
	After diet 2 wks.	231	293	548

popliteal, posterior tibial and dorsalis pedis arteries, which had been absent, were found to be of almost normal volume after the patient had been on the diet for a year. Intermittent claudication disappeared coincidently. It is possible that this was due to increased collateral circulation rather than to involution of atheroma.

During the period that this study of plasma lipoids in arteriosclerosis obliterans was being conducted, three patients were studied who had chronic occlusive disease of the arteries of their legs with slight calcification of the arteries in the roentgenograms, intermittent claudication, tuberous xanthomas of the skin and marked lipemia without diabetes mellitus. Because of the xanthomas and the very high plasma lipoids they were not included in the group of 73 cases mentioned in table 1. These patients were all

between 45 and 50 years of age. They were all given the low fat diet mentioned in the preceding paragraph and marked reduction of the plasma lipoids occurred (table 4), although patient 2 tolerated the diet rather

TABLE IV

Effect of Low Fat Diet in Arteriosclerosis Obliterans Associated with Xanthoma Tuberosum and Marked Lipemia

		Mg. cholesterol per 100 c.c. plasma	Mg. total lipoids per 100 c.c. plasma
Case 1	Before diet	667	2221
	After diet 1½ years	309	1131
Case 2	Before diet	657	1675
	After diet 5 mos.	333	1120
Case 3	Before diet	362	1604
	After diet 4 wks.	222	806

poorly and subsequently the plasma lipoids rose to levels greater than were originally obtained. Patient 1 was completely relieved of intermittent claudication and pulsations returned in the arteries of the legs after he had been on the diet one year.

In seeking an explanation for the evidence that plasma lipoids in cases of arteriosclerosis obliterans of the legs are usually but not consistently higher than normal mean values one can hypothesize that there may be two types of lesions, one seen usually in patients of middle age, in which the plasma lipoids are usually high, and one usually seen in older individuals, in which there is more evidence of degeneration of the medial coat and in which the plasma lipoids are normal or low. Another possibility to consider is that mild degrees of hyperlipemia may accelerate the development of atheroma or cause it to develop at an earlier age without being the primary cause of the lesion. This hyperlipemia may disappear with increasing age after the atherosclerosis is well developed.

SUMMARY

Plasma lipoids were studied in a series of 73 cases of arteriosclerosis obliterans without diabetes mellitus and compared with a control series of 200 individuals of various ages who were considered normal. The ranges of the various lipid fractions and total lipoids were essentially the same in the two groups. However, the mean values for all fractions and for total lipoids were definitely and significantly higher in the patients with arteriosclerosis than in the control group. Since the plasma lipoids have been shown to be essentially normal in thrombo-angiitis obliterans, it is felt that high values for plasma cholesterol and total lipoids may be of diagnostic significance in cases where the differentiation between thrombo-angiitis ob-

literans and arteriosclerosis obliterans is difficult. By the use of diets containing only small amounts of animal fat it was possible to lower the levels of the plasma lipoids definitely in four out of eight cases of arteriosclerosis obliterans where these levels were comparatively high. Three cases have been observed where there was the combination of arteriosclerosis obliterans, xanthoma tuberosum of the skin and marked lipemia.

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MUCOSAL CHANGES ACCOMPANYING GASTRIC ULCER: A GASTROSCOPIC STUDY *

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THIS study represents 317 gastroscopic observations on 91 patients, each of whom presented a definite, benign gastric ulcer. Many of these patients were examined repeatedly, as many as 27 gastroscopies being done on one case. No case of ulcer in the postoperative stomach has been included, since we did not wish to analyze mucosal changes, which might be influenced by the trauma incidental to surgery.

We used the Wolf-Schindler flexible gastroscope, in most cases the model with a 50° angle of vision, which provides greater magnification than the 85° instrument and facilitates the observation of very slight changes in the gastric mucous membrane.

Two types of mucosal alteration were found:

I. *Inflammatory Changes.* Gastritic changes range from reddening, edema, and exudation of the superficial type, to the segmentation, node-formation and erosive changes in the hypertrophic form. Atrophic gastritis with a thinned, gray or gray-green mucous membrane and visible, branching blood-vessels may occasionally be found in the ulcer-bearing stomach.^{1, 2}

II. *Purpuric Changes.* This term has been adopted for convenience, to designate mucosal hemorrhages, pigment spots and hemorrhagic erosions. Such lesions are easily recognizable in the gastric mucous membrane. Mucosal hemorrhages are discrete, round or irregular, varying in size from 1 to 5 mm. Occasionally they appear as streaks not over 1 cm. long and 2 to 3 mm. wide. Pigment spots, round or star-shaped and dark-brown in color, frequently accompany and apparently develop from the mucosal hemorrhages. Unabsorbed hemorrhages probably result in the hemorrhagic erosion which is small, but deep, and red, grayish-red or brownish-red in color.^{1, 2} So similar are these lesions to the lesions of the skin and of the mucous membranes (especially of the gastric mucous membrane) in the purpuric diseases, that the term "localized gastric purpura" has been applied.³

The relationship between the acid gastric juice and ulcer has been well studied. Also, the association of inflammation and ulcer has received some attention. However, not until the development of the flexible gastroscope

* Received for publication August 26, 1938.

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has it been possible to observe the progression and regression of mucosal changes. An analysis of the associations thus observed may be helpful in eliminating some of the obscurity surrounding the etiology of gastric ulcer. It is with this thought that this statistical study is presented.

RELATIONSHIP BETWEEN CHRONIC GASTRITIS AND GASTRIC ULCER

Konjetzny⁴ and other European workers who have made studies of resected specimens contend that all specimens examined show some type of gastritis, notably an antrum gastritis; also, that in 50 per cent of all cases a macroscopically visible, severe ulcerative antrum gastritis is present. As will be shown, it is difficult to reconcile our gastroscopic observations with these studies. We will not attempt to explain the discrepancy in this paper. Gastroscopic literature is sparse concerning the subject. Gutzeit⁵ states that rarely is gastritis not seen in ulcer cases and when absent he assumes it to be present histologically. On the other hand he states that he has never seen a case in which a gastritic ulceration changed into a true ulcer. Henning⁶ writes that in his experience, ulcer and gastritis are frequently associated. Moutier,⁷ more in agreement with this study, says, "According to our observations the ulcer usually does not develop from an ulcerative gastritis and one could consider such findings always to be secondary." These authors have not furnished statistics to substantiate their impressions.

A. In this series 43 patients or 47.2 per cent (chart 1) presented no evidence of gastritis at any examination. It must be noted that the diag-

CHART I
Presence or Absence of Inflammation In Ulcer-Bearing Stomachs

	Number	Per Cent
Absent at all examinations	43	47
Absent at first examination. Present at subsequent examinations	10	11
Present at first examination	38	42

nosis of gastritis was made even when the findings were very slight. Even so, the objection might be entered that gastroscopy does not reveal minimal changes. As evidence against this objection the following is cited: A patient was observed in whom deep roentgen-ray therapy to the stomach had been instituted. Gastroscopy revealed a definite but slight superficial gastritis, characterized by patches of adherent exudate. This patient died from coronary occlusion. The histological report read as follows: "Sections of the stomach from many areas reveal slight interstitial infiltrate of inflammatory cells with polynuclears and eosinophiles. Some of these fill the glands. A few bizarre, atypical, epithelial cells, mitoses, and multinucleated elements are seen at the level of the gland necks; particularly in the

section from the anterior wall of the body. These changes may be related to irradiation." The diagnosis was slight acute gastritis, thus confirming the gastroscopic diagnosis. Apparently then, the 50° angle gastroscope permits the diagnosis of gastritic changes of fine degree.

However, even such fine changes were not present in this group of patients. This brings up the possibility that these cases were examined during a regressive phase of the inflammation. Considering that many of these patients were examined on more than one occasion, and that no examination revealed any inflammation, this latter possibility seems unlikely.

Thus in these patients it was not possible to establish a definite relationship between the ulcer and inflammation.

B. An additional 10 patients or 11 per cent (chart 1) showed no evidence of gastritis at the first examination, but did at some subsequent examination. This sequence of events, namely, ulcer followed by inflammation, might be considered circumstantial evidence that the inflammation was incidental to the ulcer. The fact that gastritis did occur eventually, again brings up the possibility that the first examination, revealing an ulcer, might have taken place while the inflammation was in a temporarily regressive stage. Hence, we are deterred from making any statement concerning the relationship in these 10 patients, even though the order of events is highly suggestive. This group will be mentioned again.

C. A group of 38 patients or 42 per cent remains. All of these presented inflammation associated with ulcer. The priority of either could not be determined, so the cases were divided into three groups, based on the proximity of the inflammation to the ulcer (chart 2).

CHART II
Location of the Inflammation With Regard to the Ulcer

	Number
Diffuse	12
Remote	16
Adjacent	10

1. Sixteen cases (or 18 per cent of the total series) presented evidence of inflammation which was entirely remote from the ulcer. It seems inconceivable that the gastritis in these cases could be a factor in the formation of the ulcer, since in each case the ulcer area and the inflammatory area were separated by normal mucosa. There are two, more likely, explanations. First, since the incidence of gastritis was found to be 41.8 per cent in a total of 1000 patients examined gastroscopically, in these ulcer cases it might be purely a coincidental association. Second, the gastritis could quite easily be secondary to the ulcer as a result of food retention, therapy, etc.

2. In 10 cases (or 11 per cent of the total series) the ulcer was found

lying in a zone of inflammation which was circumscribed, but which varied in extent from a narrow, surrounding areola to an area of considerable diameter. In any of these cases it is quite possible that an ulcer developed on an inflammatory basis, but it is just as possible that the reverse could be true and that in some way the ulcer initiated the inflammation. We described previously 10 cases showing no inflammation at the first examination, then subsequently developing inflammatory changes. It is interesting to note that 8 of the 10 developed just such a surrounding gastritis.

3. Twelve cases (or 13 per cent of the total series) presented a diffuse inflammation involving extensive areas of the fundus or of both the fundus and antrum. One can easily consider that an ulcer might develop on such a soil. It is true that shallow erosions do occur frequently in areas of severe inflammation, but such erosions are distinctly different from a true ulcer, being neither demonstrable by roentgen-ray nor possessing the element of chronicity. They are distributed irregularly and appear and disappear with equal rapidity, quite unlike the true chronic ulcer.

Konjetzny remarks on the intimate association between ulcer and ulcerative antrum gastritis in resected specimens. In this entire series of 91 cases, in only 12 instances was an antrum gastritis observed and not one single instance of an ulcerative antrum gastritis. This type of inflammation is readily visualized gastroscopically and has been observed as a separate disease, but it has not been discovered in association with gastric ulcer.

The predilection of ulcer for the lesser curvature is well known. But, if inflammation is a precursor of ulcer and the inflammation is diffuse, we might expect to find a more general distribution of ulcer in the diffuse cases at least. Chart 3 shows the location of the ulcer in each of these 12 cases

CHART III
Location of the Ulcer in the Cases Presenting Diffuse Inflammation

	Number
Lesser curvature	10
Near lesser curvature on posterior wall	1
Posterior wall	1

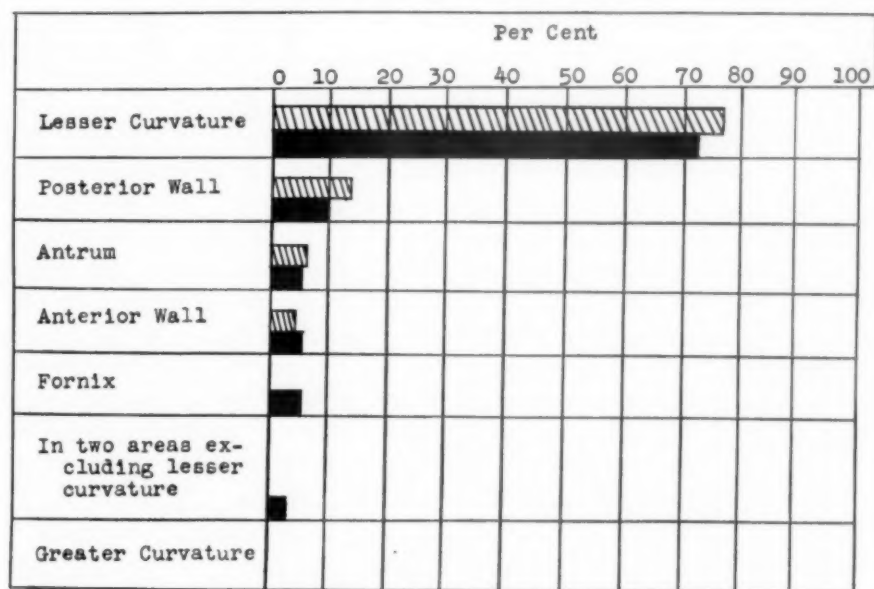
of diffuse inflammation. It is evident that, although the inflammation involved large areas of the stomach, in only one instance was the ulcer found at any appreciable distance from the lesser curvature.

Relationship Between Purpuric-Type Lesions and Gastric Ulcer. In this series, purpuric-type lesions were found in 40 of the 91 cases, an incidence of 44 per cent. When it is considered that in 1000 patients, not suffering from gastric ulcer, these lesions were found in only 5.6 per cent, it

CHART IV
Location of Purpuric Lesions

	Number	Per Cent
Lesser curvature only	15	37.5
Lesser curvature and also in some other area	14	35.0
Posterior wall only	4	10.0
Antrum only	2	5.0
Anterior wall only	2	5.0
Fornix only	2	5.0
In two areas excluding lesser curvature as one	1	2.5
Greater curvature only	0	0.0

CHART V
Illustrating Parallelism between the Purpuric Lesions and the Ulcers



Ulcer location in this series.



Location of purpuric lesions.

becomes very difficult to refrain from attaching some significance to the greater frequency in ulcer-bearing stomachs. The association of ulcer and purpuric lesions in stomachs, in which the mucous membrane is otherwise perfectly normal, is impressive. Even so, the picture may not be complete, since it is possible that, in the cases presenting no abnormality except the ulcer, the formation of this ulcer might have obliterated an initiating mucosal hemorrhage.

Chart 4 shows the location of these lesions in the 40 cases in which they were discovered. In 15 instances they were found on the lesser curvature only, and in 14 additional cases, combined on the lesser curvature and in some other area as well. In four cases, they were found on the posterior wall only and twice each in the antrum, anterior wall and fornix. On one occasion only, two areas of the same stomach other than the lesser curvature were involved.

Chart 5 shows the parallelism between the ulcer location in this series and the location of the purpuric lesions. Cases in which the lesions were found on the lesser curvature only, and those in which the lesions were multiple, being found on the lesser curvature and in some other area as well, were grouped together. The close relationship between the distribution of these purpuric lesions and the distribution of the ulcers is evident.

Theoretical considerations and the available experimental evidence concerning the pathogenesis of these purpuric lesions will not be discussed here. The interested reader is referred to articles by Castex,^{8, 9} Cushing,¹⁰ Burdenko and Mojilnitzki,¹¹ Watts and Fulton,¹² Hoff and Sheehan,¹³ and Schindler.¹⁴

SUMMARY

1. A gastroscopic study of 91 cases of gastric ulcer is presented, dealing with the relationship between certain mucosal changes and ulcer.
2. An analysis of the association of gastritis with ulcer revealed 43 patients in whom no gastritis was discovered, 10 in whom gastritis was not present at the first examination but did appear at some subsequent examination, and 38 in whom both gastritis and ulcer were found at the first examination. The theoretical aspects of these findings are discussed.
3. Purpuric-type changes were discovered in 40 patients. This incidence (44 per cent) is compared with the incidence of such changes (5.6 per cent) in stomachs, not ulcer-bearing. A parallelism between the location of these lesions and the location of ulcer has been found to exist.

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NEOPRONTOSIL (ORAL) IN THE TREATMENT OF CHRONIC ULCERATIVE COLITIS *

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WITH the advent of the various sulfamido compounds into the field of medical therapeutics it seemed reasonable, as we have stated in a previous article, to investigate the effect of these preparations on patients who have chronic ulcerative colitis.

In using the term "chronic ulcerative colitis," we are referring only to the thrombo-ulcerative form of the disease in which destructive and hyperplastic changes occur in the bowel. We felt that such a trial of therapy was justified because it seemed likely that the organism responsible for the disease might be susceptible to the effect of these sulfamido compounds. In a certain group of cases of this disease, there is every evidence of mild infectious changes limited to the distal segments of the large intestine. There is in other cases all of the evidence of severe destructive and active disease with systemic manifestations of severe toxemia. In the later stage of the disease, there is often evidence of great damage to the bowel and at times, damage to the body generally. This present group of cases embodies examples from all of these groups.

Our early brief experience seemed to indicate that sulfanilamide was of benefit in the treatment of chronic ulcerative colitis. However, as we^{1,2} pointed out later, the occasional appearance of moderate to severe toxic manifestations from the drug among patients treated made it necessary to discontinue the medication at times when the clinical status of the disease indicated the necessity for further treatment. This intolerance for the drug seemed definitely increased among many patients who were acutely ill and who had the disease in advanced stages with extensive ulceration of the colon. Then, too, the occurrence of jaundice, followed by the death of two patients who had received only moderate amounts of sulfanilamide in the treatment of chronic ulcerative colitis made us hesitant regarding the use of this drug in this condition, even though the rôle of sulfanilamide in this sequence of events was never definitely ascertained. In addition to these factors, the inherent chronicity of the disease indicated that prolonged treatment would probably be necessary, and it seemed that for this reason there would be still further opportunity to encounter deleterious effects from the drug.

For these reasons, a search was made through the field of chemotherapy for a preparation which might possess a therapeutic effect comparable to that of sulfanilamide and which at the same time would lack those factors

* Read at the New Orleans meeting of the American College of Physicians March 27, 1939.

of toxicity which would prevent its use in the treatment of chronic ulcerative colitis. We^{1,3} have mentioned elsewhere our brief trial of the dimethylated derivative of sulfanilamide which resulted in our subsequent discard of this preparation for the treatment of this condition.

Subsequently it seemed to us that neoprontosil, because of its known therapeutic efficiency and low toxicity, might offer a satisfactory solution of this problem. At that time, however, neoprontosil was available only in a 2.5 per cent solution and was given parenterally. The inherent chronicity of chronic ulcerative colitis and the necessity for long continued use of any therapeutic measure made it apparent that parenteral administration was impractical. Then too, as was shown by Rosenthal and his co-workers,⁹ 85 to 95 per cent of this drug, when given parenterally to experimental animals, was excreted at the end of five hours. Thus, both of these facts made it apparent that under existing conditions, first, only small amounts of neoprontosil could be made available for use and second, that even if repeated injections were feasible, it did not seem possible that effective concentrations of neoprontosil could be maintained satisfactorily in the body for any prolonged period.

A review of the experimental work of Raiziss et al.,⁸ and of that of Rosenthal and his co-workers, working independently, indicated that if the drug could be given orally it would be retained in the body for a longer time and thus would be more slowly absorbed. It seemed that such conditions would allow for a greater concentration and therefore, greater therapeutic efficiency. Experimental work among animals indicated that this increased efficiency occurred with oral administration.

For these reasons, it seemed to us that a clinical trial of neoprontosil (oral) was justified in cases of chronic ulcerative colitis. The early experience with this drug, which was dispensed in powdered form in a capsule, had previously been reported and this led us to believe that further treatment with this preparation was justified.

The dosage employed was similar to that used previously when sulfanilamide was administered in our treatment of patients who had this disease. To the average adult, amounts of 4 to 5.5 gm. of this drug, divided into five equal parts, were given in each 24 hours. In other words, 15 grains (1 gm.) were usually given an hour before each meal, at bedtime (10 p.m.) and at 3:00 a.m. in order to maintain a uniform concentration throughout each 24 hours. Such a course was administered usually for 10 to 14 days. It was found that if the drug is given an hour before the intake of food, most of the gastrointestinal symptoms usually associated with sulfamido compounds will be eliminated.

In many instances in the more stubborn cases, subsequent to such a course, experience has indicated that an additional course in smaller dosage, approximately 2.5 gm. given daily for another 10 to 14 days, is advisable. In the majority of instances, however, a complete rest from the drug for seven to 14 days was prescribed—between each course of therapy. In a

few cases in which the disease seemed particularly recalcitrant to treatment doses of 4 to 5.5 gm. daily were given continuously for a period of 21 to 28 days without any disagreeable effect save for the occasional presence of some sensation of mild fatigue. In general, a procedure of this type was followed in all of these cases for at least the first three months of treatment and then as improvement occurred the daily dosage was reduced and the periods without the drug were lengthened.

In the present paper, we are reporting on our use of neoprontosil (oral) in a series of 48 patients. Of this number, 29 unselected patients form a part of the report, in which major therapy was restricted to neoprontosil alone (group A). In the remaining 19 cases serum or vaccine was used in conjunction with neoprontosil (group B).

For purposes of comparison and to conserve space, in several instances we have used the familiar standard of grading, 1 to 4, 1 denoting minimal and 4 maximal involvement. Thus, in referring to the extent to which the disease has involved the bowel, as revealed by roentgenologic examination, we have referred to involvement of rectum and sigmoid alone as grade 1. Involvement of the large intestine including the rectum, sigmoid and colon as far as the splenic flexure we have called grade 2; involvement to the hepatic flexure, grade 3, and when the entire large intestine was involved we have used the term, grade 4. Grade 4 plus refers to involvement of the entire colon and terminal portion of the ileum. We have used this same form of comparison for grading the degree of severity of the disease. In all of these cases search has been made for other possible causes of the ulceration of the bowel and in every instance stools have been found free of parasites and ova. It should be pointed out that space does not permit a detailed analysis of each case; therefore the several groups are presented in tables 1 and 2.

In these tables the heading "duration of disease, years" fails to express that the disease may have existed intermittently, and that treatment with neoprontosil was carried out only since the time of the exacerbation which preceded admission to the clinic. Some form of therapy on a symptomatic basis or therapeutic agents such as serum or vaccine, had been given to the majority of these patients at some previous time. In some instances, such treatment had been followed by temporary remission of the disease but in every case the disease was active at the time when treatment with neoprontosil was started by us. It is evident that individual variations in the severity of the disease cannot be accurately described. Thus, it is possible to have involvement of the entire large intestine with objective evidence of only moderate activity and at the same time find great variations, in different instances, of the actual clinical severity of the disease. The column "total duration of treatment, months," in the table refers to the period during which these patients were under treatment with neoprontosil. In most instances, this represents a period of two or four weeks at the clinic and subsequent treatment at home. In many instances, the patients lived near

enough so that they could return for observation at intervals of two or four weeks. It can be seen that the patients in group A (table 1), were under treatment and observation for six weeks to 19 months and those in group B (table 2) from four weeks to 12 months. In every instance where possible we have continued therapy with neoprontosil even when the disease appeared

TABLE I
Chronic Ulcerative Colitis: Data on Treatment with Neoprontosil (Oral); 29 Cases

Group A			Duration of disease, yrs.	Daily number of stools with blood	Roentgenologic evidence of extent of involvement of colon	Findings at initial proctoscopic examination			Clinical severity	Total duration of treatment, months	Findings at last examination		
Case	Sex	Age, yrs.				Activity	Contraction	Bleeding			Symptomatic Clinical status	Stools daily	Objective On proctoscopic examination
1	M	56	8	5-14	4	2	2	3	2	5	Improved	3-4	"Grade 1"
2	M	38	4	10-15	4	3	3	2	2	6	Improved	3	"Activity minimal"
3	F	38	10	4-9	4	2	2	3	2	14	Inactive	1	"Activity minimal"
4	F	30	7	8-10	4	1	1	1	2	3	Inactive	2-3	"Mucosa appears normal"
5	F	37	2	5-11	4	1	0	1	2	5	Improved	2	"Activity minimal"
6	M	47	7	6-8	4	1	1	2	2	4	Improved	5	"Very little activity"
7	M	36	6	6-8	4	2	0	1	2	13	Inactive	1-2	"No ulceration, no contraction, no bleeding"
8	M	23	6	1-6	4	2	2	1	2	2	Improved	2	"Grade 1"
9	F	43	5	3-10	4	1	1	2	2	3	Inactive	1-2	"Activity minimal"
10	M	41	$\frac{1}{2}$	5	4	2	2	2	2	2	Improved		
11	F	44	6	3-8	4	1	1	1	1	2	Unimproved	3-8	
12	F	29	1	4	2	2	0	3	2	7	Inactive	1-2	"Activity minimal"
13	M	49	8	12	2	2	0	2	2	3	Improved	2	"Activity minimal"
14	F	35	1	4-9	1	2	1	1	2	10	Inactive	1	"Grade 1"
15	M	22	4	6-7	1	2	0	3	2	$1\frac{1}{2}$	Unimproved	6	"Slight ? improvement"
16	M	18	4	2-3	1	1	0	1	2	$1\frac{1}{2}$	Improved	2-3	"Activity minimal"
17	F	58	28	1-2	1	1	0	2	2	2	Improved	1-2	"Very definite improvement but some evidence of disease"
18	F	29	3	4-8	1	2	0	2	2	8	Inactive	1	"Normal mucosa"
19	M	52	9	4-6	1	2	1	0	2	5	Inactive	1	
20	F	26	2	5-10	1	1	1	1	2	5	Improved	2-3	"Activity minimal"
21	F	30	9	3-15	1	1	1	2	2	19	Inactive	1-2	"Process quiescent"
22	F	61	2	8-10	1	2	2	1	2	17	Improved	6-7	"Grade 1"
23	M	35	$\frac{1}{2}$	2-14	1	1	0	2	2	2	Improved	2-3	
24	M	21	$1\frac{1}{2}$	2-5	1	1	0	1	1	17	Inactive	2-3	"Activity minimal"
25	M	48	5	2	1	1	1	1	1	8	Inactive	1	"Normal mucosa"
26	F	43	1	1-2	1	2	0	2	1	2	Inactive		"Very slight granulation anterior wall, otherwise negative"
27	F	72	$\frac{1}{4}$	1-2	1	1	1	2	1	2	Unimproved	1-2	"Same as original"
28	M	31	8	6	1	1	2	2	1	2	Inactive	2	"Activity minimal"
29	M	41	11	4	1	1	0	1	1	1	Improved	2	

TABLE II

Chronic Ulcerative Colitis: Data on Treatment with Neoprontosil (Oral) Plus Serum or Vaccine; 19 Cases

Group B			Duration of disease, yrs.	Daily number of stools with blood	Roentgenologic evidence of extent of involvement of colon	Findings at initial proctoscopic examination			Clinical severity	Total duration of treatment, months	Findings at last examination		
Case	Sex	Age, yrs.				Act-ivity	Con-trac-tion	Bleed-ing			Symptomatic	Stools, daily	Objective
30	F	21	4	13	4 plus	2	2	1	3	2	Unimproved	1-2	"Normal"
31	M	21	4	12	4 plus	2	2	2	3	4	Unimproved	10	
32	M	25	4	9	4 plus	1	3	1	3	4	Unimproved	8	
33	M	23	2	12	4 plus	1	3	1	2	6	Unimproved	9	
34	F	17	1½	9	4	2	1	2	3	3	Inactive	1	
35	F	25	8	15	4	1	2	1	3	12	Improved	7	
36	M	18	3	12	4	2	2	2	1	2	Improved	4	
37	F	30	2	5	3	1	1	1	1	2	Improved	3	
38	M	27	4	5	3	1	1	1	1	1	Inactive	1	
39	M	42	7	7	2	1	1	2	3	2	Inactive	1	
40	F	24	½	8	2	1	0	2	2	2	Inactive	1	
41	M	12	5	6	2	2	2	2	2	3	Unimproved	6	
42	F	38	9	5	2	1	0	2	1	2	Improved	3	
43	F	24	3	9	1	3	0	2	3	2	Inactive	2	"Activity minimal"
44	F	35	2½	4-5	1	2	1	1	1	2	Inactive	1-2	
45	F	20	1	10	1	1	0	2	1	2	Improved	3	
46	F	13	¾	14	1	2	1	1	1	1	Inactive	1	
47	M	32	8	2	1	2	1	1	1	2	Improved	1	
48	F	16	½	12	*	3	0	2	3	2	Inactive	2	

* Examination not performed.

quiescent for one or more months. All proctoscopic examinations were made in the Section on Proctology at The Mayo Clinic.

In the analysis of the data obtained from a study of the results of treatment, the following classification of final results has been adopted. Three major groups of results appear in the analysis: (1) The group of cases in which the results could be considered excellent; (2) the group in which the results could be considered fair and (3) the group in which the results were considered poor or unsatisfactory.

ANALYSIS OF GROUP A

Group A was composed of 29 patients who received neoprontosil only. Of the patients in this group 15 were males and 14 females. The youngest patient was 18 years of age, the oldest 72 years of age; the average age was 39.4 years. Thirteen patients (44.8 per cent) obtained results which could be classified as excellent; 13 patients (44.8 per cent) obtained results which could be considered fair and only three patients (10 per cent) obtained results which were considered poor.

Two types of results appear in that group of results classified as excellent. The first type is that in which the disease at this time of evaluation was considered symptomatically (clinically) and objectively (proctoscopically) inactive. There were five such patients (cases 4, 7, 18, 21, 25). The second type of excellent result was in that group in which the disease was symptomatically inactive, of which there were eight patients (cases 3, 9, 12, 14, 19, 24, 26, 28). Six of these patients (cases 3, 9, 12, 24, 26, 28) had a final proctoscopic examination which showed that the activity of the disease was minimal. One patient (case 19) is included in this group because he did not have a final proctoscopic examination. One patient (case 4) had objective evidence of inactivity for several months; the disease became active, grade 2, during an acute respiratory infection and at the time of the last examination was symptomatically inactive although objectively (proctoscopically) the activity was graded 1.

The group in which fair results occurred includes those patients in whom definite improvement followed treatment, yet the final result was not good enough to be interpreted as complete inactivity of the disease. However, seven (cases 2, 5, 6, 13, 16, 17, 20) of the thirteen patients (cases 1, 2, 5, 6, 8, 10, 13, 16, 17, 20, 22, 23, 29) who appear in this group had a final proctoscopic examination which revealed minimal activity of the disease. In case 22, proctoscopic reexamination showed activity, grade 2; in two others (cases 1 and 8), there was activity, grade 1 and in three others (cases 10, 23, 29) a final proctoscopic examination was not made.

The third group of results which were classified as poor in which three cases appear deserve further mention. In case 27, the patient was an elderly woman; the disease which was limited to the rectum and sigmoid, was classified as grade 1. Initial response of the disease to the drug was favorable but treatment was abandoned after the patient returned home because of difficulty of obtaining the drug at a time when it was not yet on the market. The amount of the drug given, therefore, was inadequate.

In case 11 of this group, the disease involved the entire colon but was graded 1 although the symptoms had been comparatively constant. Up to this time, this patient has been under observation for only two months and has received but two courses of treatment of 14 days each. The duration of treatment thus far must be considered inadequate but it is questionable whether much can be accomplished for a condition of this type with extensive changes in the bowel owing to persistent chronic diseases.

The third patient (case 15) failed to show a satisfactory response after six weeks of treatment at the clinic, although there was a slight suggestion of improvement in the mucosa of the bowel. An adequate explanation cannot be offered for this failure. Experience with chronic ulcerative colitis has shown an occasional case similar to this which is refractory to any form of therapy.

It is notable that in this series of cases the amount of bowel involved did not seem to affect materially the final clinical result when adequate treat-

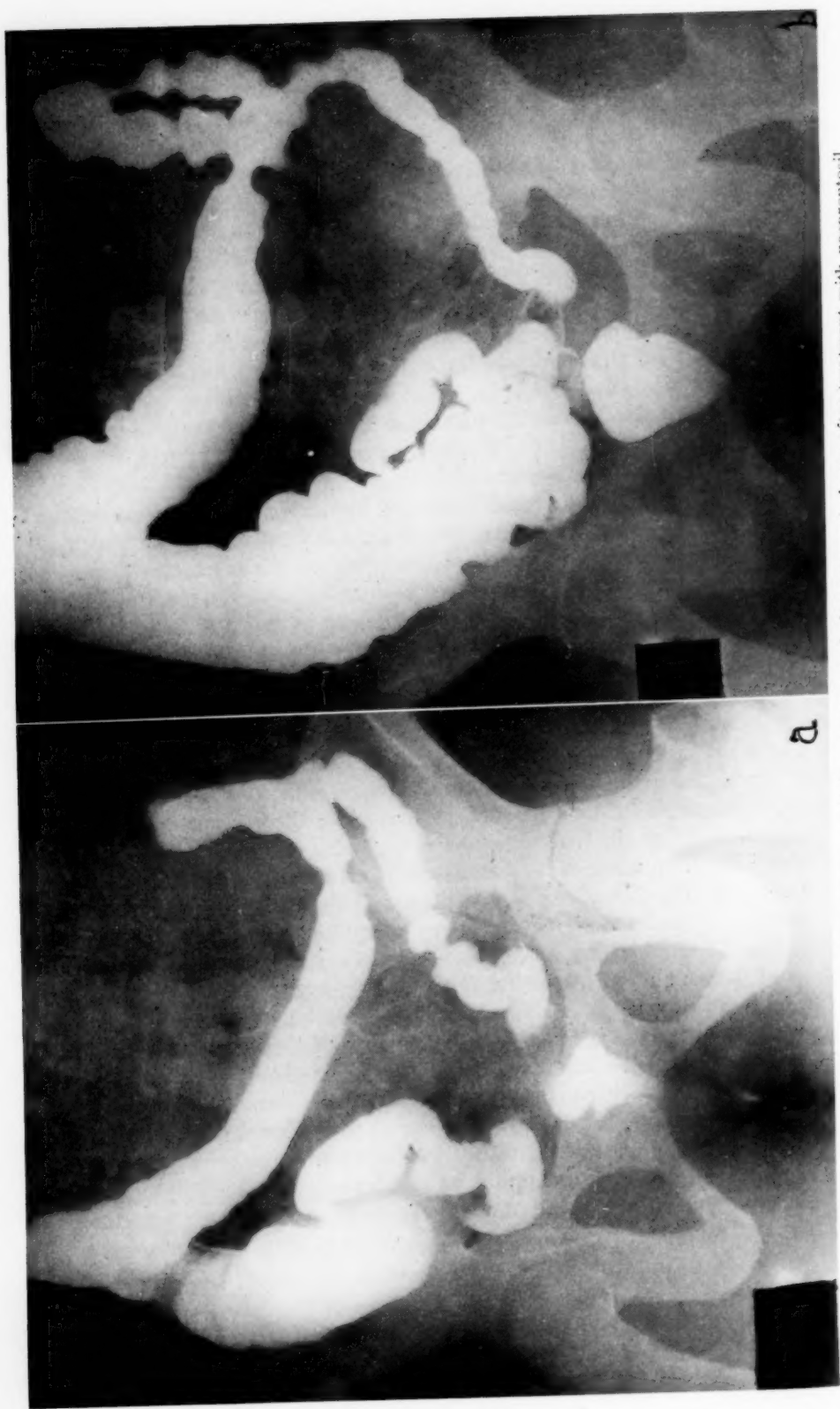


Fig. 1. Roentgenograms of the barium enema. *a*, Before treatment; *b*, improvement shown after treatment with neoprontosil.

ment was carried out provided that active destruction of the bowel was not too great. For example, there were 11 patients who had involvement of the entire colon, grade 4, and in this group there were 10 cases in which the activity was of grade 2. Case 3 illustrated in figure 1 shows the improvement manifested roentgenographically in the large intestine following the use of neoprontosil. In two of these cases the disease, symptomatically and objectively, was inactive at the time of the last examination. In three others the disease was inactive symptomatically and in five, definitely improved. The one patient in this group whose condition did not improve was the patient previously cited whose treatment has thus far been too inadequate to arrive at a satisfactory evaluation. Involvement of the colon, grade 3, did not occur in any patients of group A, but there were two patients who had involvement as far as the splenic flexure, grade 2. The activity of the disease in these cases was graded 3 and 2; the final results showed the disease to be symptomatically inactive in one instance and improved in the other. Objectively both showed only minimal activity.

In the group of sixteen patients in which the disease was limited to the rectum and sigmoid, grade 1, and in which the activity of the disease was graded 1 to 2, in three the disease was symptomatically and objectively inactive at the time of the final examination. In five others the disease was symptomatically inactive; in six cases improvement had occurred and in two previously mentioned, treatment was a failure. Although not shown on the chart, it is further interesting to note that among those individuals in this group whose stools were very bloody and were increased in number, four to 15 daily, both the quantity of blood and the number of stools were in most instances greatly decreased on the third to the fifth day of treatment. In other words, blood disappeared from the stools of these individuals long before healing of a severely denuded bowel would have seemed possible. It is also interesting that the appearance of the mucous membrane proctoscopically in a number of cases was reported greatly improved and in some instances was even normal as early as two or four weeks after the beginning of treatment.

Of special interest in this series of cases are two in which there occurred the unusual complication of pyoderma gangraenosum, an ulcerated condition found in association with chronic ulcerative colitis and which has been described by O'Leary, Brunsting⁴ and one of us (Bargen²). In case 17, the ulcer which involved the right leg between the knee and ankle had begun to develop six weeks prior to admission to the clinic, at the time of an exacerbation of the colitis. Organisms were not recovered from it on culture. After 15 days of treatment with neoprontosil remarkable healing of the ulcer occurred. Symptomatic and objective improvement of the ulcerative colitis also took place. After this patient's return home, treatment with neoprontosil was temporarily abandoned due to difficulty in obtaining the drug. When the patient was last heard from the ulcer was incompletely healed but had shown no advancement (figure 2). The second



FIG. 2. Pyoderma gangraenosum. *a*, Before treatment with neoprontosil (oral); *b*, extent of healing after treatment (case 17).

patient (case 4) first noticed an ulcer of the left leg one month prior to admission to the clinic. It occurred after local trauma and an acute respiratory infection. At the time of admission, the ulcer was 3 cm. in diameter and possessed undermined edges; organisms were not recovered from it on culture. The chronic ulcerative colitis involved the entire colon and its activity on proctoscopic examination was graded 1 +. The patient's temperature was 102° F. (38.9° C.) and the leukocytes numbered 22,000 per cubic millimeter of blood. After only four days of treatment with neoprontosil plus the use of scarlet red ointment locally, the inflammation in the border of the ulcer subsided and healing occurred. The temperature and the number of leukocytes returned to normal after seven days. After 14 days, healing had progressed to a stage at which it was felt advisable to dismiss the patient.

At this time, treatment with neoprontosil was discontinued for a period of two weeks and during this interval the ulcer of the leg recurred and rapidly increased in size. The patient returned to the clinic five weeks later and again was acutely ill. The ulcer at this time involved the leg

from the knee to three inches above the ankle, with the exception of an intervening longitudinal bridge of unaffected tissue 5 cm. wide (figure 3). Neoprontosil was again given in doses of 5.5 gm. daily. After five days the temperature and number of leukocytes again returned to normal and the general condition was much improved. The ulcer, however, showed no



FIG. 3. Pyoderma gangraenosum subsequent to use of neoprontosil (oral) showing extent of involvement by ulcer and degree of healing (case 4).

definite evidence of healing over a period of 14 days. During this time the involvement had spread so that the band of previously described intervening tissue had narrowed to 1 cm. Improvement was then noted and the borders of the ulcer lost their inflammatory appearance. Improvement continued in a remarkable manner and at the end of three weeks the ulcer was en-

tirely healed save for a few minute denuded areas. Proctoscopic examination at this time showed the intestinal mucosa to be entirely normal save for the presence of some scarring (table 2).

ANALYSIS OF GROUP B

Group B was composed of 19 patients who received neoprontosil plus serum or vaccine. Of the patients in this group, eight were males and 11 females; through mere chance these patients were considerably younger than those in group A. The youngest patient was 12 years of age and the oldest, 42 years; the average age was 24.3 years. In eight cases (42 per cent) in this group (cases 34, 38, 39, 40, 43, 44, 46, 48) results were classified as excellent because the disease was symptomatically inactive. In two of these cases subsequent proctoscopic examinations were performed; in one (case 40) the mucosa was healed and in one (case 43), there was minimal activity of the disease.

An opportunity for final proctoscopic examination of the other six patients did not occur. Their condition was improved when they were dismissed from the clinic and subsequent reports revealed that they were free of symptoms. Two of these (cases 34 and 48) deserve special comment, girls of 17 and 16 years of age respectively, who had been severely ill for weeks with marked symptoms of sepsis and toxemia and with temperatures of 104° F. (40° C). Two weeks after the administration of neoprontosil, in the usual manner, their temperatures had receded to normal, the rectal discharges had been greatly reduced and the blood in the stools had diminished to a great extent. It should be noted that whereas involvement of the bowel of one patient was extensive the other patient was too ill for roentgenologic examination. In both cases the duration of the disease was brief but the disease was moderately acute. In case 10 in group A a similar type of disease was present with symptoms of sepsis and a similar response to neoprontosil occurred.

Six (32 per cent) patients (cases 35, 36, 37, 42, 45, 47) obtained results which were fair. That is, they were definitely improved symptomatically but this could not be evaluated objectively because final proctoscopic examinations were not made.

All five patients (26 per cent) (cases 30, 31, 32, 33, 41) who were unimproved had extremely advanced disease. They all showed evidence of severe destruction of the entire large intestine and terminal portion of the ileum, or serious complications of the disease.

In case 30 there was involvement of the entire large bowel and terminal portion of the ileum, nutritional edema and a rectovaginal fistula with other fistulas near the anus. In case 31 there was involvement of the entire large bowel and terminal portion of the ileum and the whole segment was an irregular tube about 1 to 1.5 cm. in diameter. In case 33, in addition to the ulcerative colitis, annoying gastrointestinal allergic manifestations to food-

stuffs occurred. In case 32, there was a very marked secondary anemia with an associated toxemia. General improvement occurred in this case with improvement of the anemia and with a gain of 15 pounds, but little change took place in the symptoms from the bowel. Our experience with other similar cases reveals instances in which the same type of response followed treatment. In case 41, the patient, aged 12 years, had in addition to chronic ulcerative colitis a cerebral lesion, either an abscess or a brain tumor. After some temporary improvement he suffered a subacute perforation of the sigmoid.

COMMENT

In addition to the foregoing clinical appraisal of these cases, there are certain points of general interest in connection with this form of therapy. One of the most important of these is the general lack of toxic manifestations which might be attributed to the use of neoprontosil. This observation in this group of cases of chronic ulcerative colitis is in accordance with the previous experience of Herrell and Brown⁵ with the use of this drug in the treatment of more than 500 patients who had various types of infections. Although minor degrees of malaise, fatigue and headache were noted at times during the treatment of chronic ulcerative colitis with neoprontosil the symptoms were never of a degree sufficient to necessitate withdrawal of the drug and but rarely were of a nature requiring a reduction of the prescribed doses. As aforementioned, general systemic manifestations of intolerance are exceedingly rare in all cases in which neoprontosil is used; however, there is a tendency to local irritation of the bowel; cramps or diarrhea may occur at times when large amounts of the drug are given, for instance amounts in excess of 5.5 gm. daily. We feel that an explanation for this irritation rests on the probability that the bowel is receiving larger amounts of the drug than it is able to absorb and that some local irritation is thereby produced.

We have also encountered a similar effect but a temporary one among certain patients who had chronic ulcerative colitis, particularly those who had involvement of the entire colon with deformity and scarring. In such cases the drug at times produced cramps and exacerbation of the diarrhea but these symptoms promptly subsided when the medication was discontinued. Under a reduced dosage, 2.5 gm. or 3.5 gm. daily, such patients have been able to continue with treatment until material improvement has occurred. Two patients, who were not under our direct observation at the time, experienced a mild rash of questionable type and treatment was discontinued temporarily. Nausea and emesis also occurred temporarily in several cases. Cyanosis did not occur in any of these cases although, occasionally, small amounts of methemoglobin and sulfhemoglobin were detected in the blood by spectroscopic analysis. In no instance was there noted any significant decline of the carbon dioxide combining power of the blood plasma despite the fact that these patients did not receive alkalis with the

drug. In the entire group of patients the content of hemoglobin, and the number of erythrocytes and leukocytes in the blood did not show any significant untoward changes which could be attributed to the use of neoprontosil. In some instances transfusions were given because of an already existing anemia that resulted from loss of blood or from toxemia. Repeated examination of the urine of these patients did not show evidence of renal irritation attributable to neoprontosil.

It is of interest that the estimation, according to the method of Marshall,⁷ of the concentration of sulfanilamide in the blood of these patients while receiving neoprontosil varied as a rule between 0.9 and 3.6 mg. per 100 c.c. of blood and that the average value was 2.4 mg. Although these estimations are lower than those usually encountered among patients receiving similar amounts of sulfanilamide, nevertheless we believe that they constitute definite evidence of the absorption of orally administered neoprontosil. Examination of the urine of these patients showed the presence of free sulfanilamide in concentrations of 46 to 69 mg. per 100 c.c. and conjugated sulfanilamide in concentrations of 31 to 56 mg. per 100 c.c. These estimations of sulfanilamide in the urine also are appreciably lower than those which are found when sulfanilamide is administered in similar doses.

It seems proper at this point to emphasize an observation which we made previously regarding the use of neoprontosil in cases of ulcerative colitis; namely, that it is not possible for any chemotherapeutic agent to restore to normal the physiologic function of a bowel which has become contracted and deformed by the presence of disease of long standing. Obviously under such circumstances all that any such drug can be expected to accomplish is the control of symptoms that are due to active infection; those symptoms which result from altered function of a deformed bowel must be expected to continue to disturb the patient. If, however, neoprontosil is used early in the course of chronic ulcerative colitis, it seems evident that the maximal effect from the drug will be obtained.

At present, only impressions exist concerning the mode of action of neoprontosil in the treatment of chronic ulcerative colitis. Certainly we do not feel that the therapeutic response can be explained on the basis of the sulfanilamide which is made available to the systemic circulation by the breakdown of neoprontosil. In other words, as we have suggested previously, it would appear that neoprontosil possesses an action which is wholly independent of and in addition to that of the sulfanilamide which it liberates. The recent experimental work of King and his co-workers⁸ tends to substantiate this impression. Although the experimental work of Marshall indicates that neoprontosil is not absorbed by the large bowel of animals, it seems likely that this absorption occurs in the large bowel of man. It also seems possible that the mere presence of the drug in direct contact with the mucous membranes of the bowel may exert a local action independent

of that made possible by absorption of the drug by mucous membranes or by the presence of the drug in the systemic circulation.

It is important to emphasize that experience with chronic ulcerative colitis has shown that it is a disease characterized by spontaneous exacerbations and remissions. We believe, however, that the prompt improvement of these lesions which has occurred so frequently and uniformly after the use of neoprontosil justifies the conclusion that the drug is of definite benefit in this disease. It follows, however, that the tendency of the disease to recur must be appreciated fully in treating this condition. Therefore, in every instance we have continued to give intermittent courses of treatment even when the disease has been symptomatically and objectively inactive for some months. The lack of toxic manifestations associated with the use of neoprontosil in general makes this drug especially adaptable to the treatment of chronic ulcerative colitis.

SUMMARY

A clinical study has been presented in an attempt to evaluate the effectiveness of neoprontosil (oral) in the treatment of 48 patients who had chronic ulcerative colitis. For the purpose of further evaluation of therapy one group comprising 29 patients (group A) received neoprontosil only. Another group of 19 patients (group B) received, in addition to neoprontosil, either vaccine or serum.

It appears that 44.8 per cent of the patients in group A obtained clinical results which could be classified as excellent; that 44.8 per cent obtained results which could be considered fair and that failure of treatment or poor results occurred in only 10 per cent of cases.

The analysis indicates that 42 per cent of patients in group B obtained results which were considered excellent whereas 32 per cent obtained results which may be considered fair. Failure of treatment or poor results occurred in 26 per cent of this group. It should be noted that the two groups are not identical as regards severity of the disease; nevertheless the results seem significant.

It is also of significance that the clinical response to neoprontosil is not predictable on the basis of the amount of bowel involved by the disease so long as destruction of the bowel is not too great.

We are exceedingly anxious not to create the impression that neoprontosil is a specific remedy for chronic ulcerative colitis. However, it is reasonable to deduce from the results herein reported that the lack of toxic manifestations associated with the use of this drug and the comparatively encouraging clinical responses amply justify the use of neoprontosil (oral) in the treatment of chronic ulcerative colitis.

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CASE REPORTS

THE RESPONSE OF ACROMEGALY TO DEEP ROENTGEN-RAY THERAPY: A CASE REPORT *

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THERE is ordinarily no difficulty associated with the diagnosis of typical acromegaly. Following the classical descriptions by Marie,¹ the disorder became recognized as one of rather frequent occurrence. Nevertheless, the treatment of acromegaly has remained unsatisfactory. Occasionally the underlying pathological changes in the pituitary are such that the symptoms and signs are chiefly those of a space-occupying, hypophyseal tumor. Under such circumstances and especially when vision is threatened by pressure on the optic chiasma, the inclination is to regard and treat the disorder from the view-point of tumor formation rather than hormonal dysfunction. On the other hand, when signs of a space-occupying mass are absent and no involvement of cranial nerves occurs the abnormal constitutional manifestations of hypophyseal dysfunction dominate the therapeutic problem and treatment is non-surgical.

In the patient whose case report follows the symptoms and signs of an intracranial tumor were present in association with manifestations of hypophyseal dysfunction.

CASE REPORT

B. A., a white female, now 40 years of age, first came to the Vanderbilt University Hospital in April 1928. She complained of amenorrhea of six years' duration.

The menarche had occurred at 13; the periods were regular, occurred in a 28 day cycle and were normal in character.

In September 1922, when she was 24 years old, the menses ceased abruptly. In 1926, she first noted changes in the facial characters; the features gradually became coarse, the nose broad, the lips thickened and the eyes more prominent. Her voice became husky. She experienced pains in her fingers and she noted an increase in the size of her hands and feet. She now wore size 9 gloves and size 6 shoes whereas formerly, her glove size was 6 and shoe size 3. In 1924 at the time of a tonsillectomy she was told that the thyroid was enlarged. Since that time the gland has not increased in size. Members of her family felt that she had recently become nervous and emotionally unstable. Her appetite had been good though not excessive and she had lost no weight. During 1926 and 1927 she felt exhausted and experienced great difficulty in continuing to work in a shoe factory.

She married in 1926 and her husband was living and well. There had been no pregnancies. Contraceptives had not been used.

For a year prior to admission to the hospital she had experienced frequent headaches which she localized behind the eyes and she had been conscious of eye strain associated with lacrimation. During the month preceding her admission head-

* Received for publication June 6, 1938.

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ache became constant. She localized the discomfort chiefly in and about the left eye. Vomiting had occurred occasionally in association with headache.

Her past health had been good. Her father and mother were living and well. She had four siblings. One sister had diabetes. No disease had appeared with unusual frequency in her family.

Physical examination (April 1928): Temperature 98.6° F., pulse 84, height 65.6 inches (166 centimeters), weight 135 pounds (61.4 kg). The facial characters were considered typical of acromegaly. (Figure 1.) The voice was coarse and deep. The



FIG. 1. Photographs of patient made in 1920 and 1928.

mental functions were normal. The fingers were thicker and shorter than normal. The skin was coarse; the hair, while coarse, was normal in distribution. The thyroid was diffusely enlarged. It contained no nodules, and no thrill or bruit was present. Lid lag and slight failure of convergence were noted. The eyes were prominent, exophthalmos being more marked on the left. The pupils reacted normally. The fundi were normal. There was no evidence of increased intracranial pressure. There was slight prognathism. The teeth and tongue were normal. The bony thorax was normal save for the changes usually associated with slight emphysema. The heart and lungs were not remarkable. The blood pressure was 105 systolic, 80 diastolic. The abdomen was normal as were the external genitalia. The body of the uterus was quite small. The cervix was normal. The neurological examination revealed normal muscle tone and strength. No vasomotor abnormalities were noted. The deep reflexes were normal as were position and vibration perception. No pathological reflexes were present.

Cranial nerves: there was a marked difference in the sense of smell on the two sides; on the left, neither vanilla, coffee, peppermint nor vinegar could be identified, while on the right side all odors except coffee were recognized and were described as much more intense. Visual acuity was normal but perimetric charts of the visual fields revealed slight, definite temporal constriction. The latter was more pronounced when red and green targets were used. The urine was normal.

The red blood cell count was 4,880,000, the hemoglobin 93 per cent (Sahli). The white blood cell count was 7,850 of which 57 per cent were neutrophils, 37 per cent lymphocytes and 6 per cent monocytes. The blood Wassermann test was negative.

The basal metabolic rate was plus 17 per cent.

A glucose tolerance test was performed using 1.5 grams glucose per kilo of weight: the fasting blood sugar was 114 mg. per cent, after one hour 142, two hours 133, three hours 86, four hours 80, five hours 78. All urine specimens collected during this period gave negative tests for glucose.

Roentgenograms of the skull revealed marked enlargement of the sella turcica with hypertrophy of the posterior clinoid process. (Figure 2.) No changes were

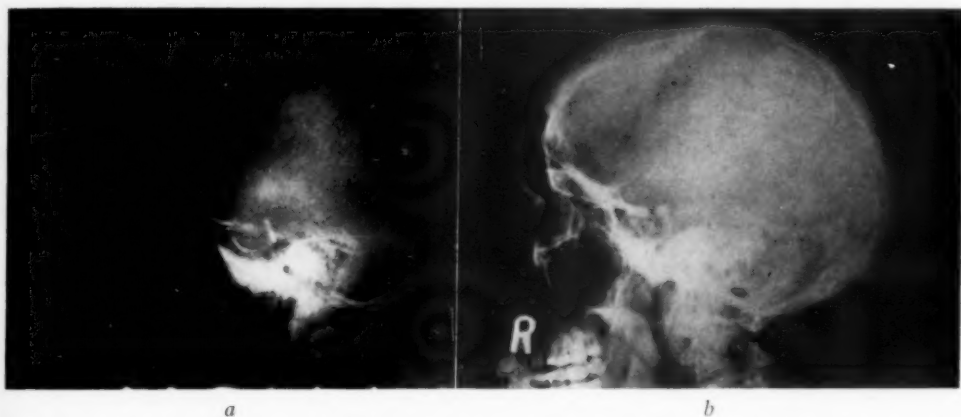


FIG. 2. *a*. Roentgenogram, 1928, showing marked enlargement of the sella turcica and hypertrophy of the posterior clinoid processes. *b*. Roentgenogram, 1938, showing no significant change from the 1928 film.

noted in the bones of the hands and feet. All the sinuses and especially the frontals were large. The chest plate revealed no abnormalities.

It appeared evident that the patient had an adenoma of the pituitary with acromegaly and there was evidence of pressure on the optic chiasma and dysfunction of the left olfactory tract. It was decided to treat her by means of roentgen-rays and accordingly on May 2, 1928 she was irradiated over the pituitary region. The treatment consisted of 20 milliamperes for 15 minutes through a $\frac{1}{2}$ millimeter copper and one millimeter aluminum filter. This was delivered through an 8 centimeter portal at a distance of 50 centimeters. The roentgen-ray machine was a 200,000 volt apparatus, and the dose delivered was 300 milliampere minutes, amounting to approximately 800-900 'R' (with "back-scatter"). This treatment was given on each of two successive days in April and on June 28 and June 30, 1928 the treatment was repeated. Following these roentgen-ray treatments the patient felt definitely improved.

She was re-admitted to the hospital in October 1929 for the removal of a pedunculated sebaceous cyst of the left leg. In the interval since her last admission she had experienced no weakness, irritability, headache or visual disturbance. On this second hospital admission the physical examination and the laboratory data were essentially unchanged. The basal metabolic rate was now plus 23 per cent. A glucose tolerance test was as follows: The fasting blood sugar was 75 mg. per cent, after one hour 125, two hours 108, and three hours 62. The urine volume for 24 hours was 2,910 c.c. The visual fields were essentially normal. The visual acuity was 20/20 in each eye and roentgenograms of the sella turcica showed no change



FIG. 3. Photograph of patient, April 1937, with her 14 month old son.

when compared with the films of May 1928. Although there were no positive indications for further roentgen-ray treatment she was given empirically a fifth and final treatment of approximately 1,000 'R' on September 18, 1929.

During the next four years the patient appeared in the out-patient department with minor ailments. She was working and apparently felt greatly improved. She had

been less nervous and had not suffered with headache. There had occurred no visual disturbances and the sense of smell had been normal. No change in the size of her gloves or shoes had occurred.

In 1932 she experienced the return of libido. Her menstrual cycle became re-established and was in every way normal.

In August 1933 she was readmitted to the hospital because of acute bronchitis. There was no evidence of any progression in the skeletal abnormalities. The basal metabolic rate was minus 3 per cent.

In February of 1935, she was seen in the endocrine clinic because of amenorrhea of three months' duration. The uterus was found to be slightly enlarged. Roentgen-rays made at this time showed widening and tufting of the ends of the phalanges of all the fingers. There was no essential change in the sella turcica. The visual fields and acuity were normal. A few weeks later she fell and a miscarriage occurred. In April 1935 she had a normal menstrual period. In August 1935 she visited the obstetrical clinic because she had failed to menstruate since May. She was found to be pregnant. She returned at regular intervals to the obstetrical clinic and was observed throughout a normal pregnancy. She was admitted to the Vanderbilt Hospital on February 25, 1936, and, after a fairly difficult labor because of a posterior position, was delivered of a normal male infant. The baby weighed eight pounds and 10 ounces, and breathed spontaneously. The puerperium was normal.

The patient was examined in April 1937 and there was no evidence of any progression in the pituitary disorder. (Figure 3.) The findings on physical examination were essentially unchanged. The blood pressure was 94 systolic and 66 diastolic, the basal metabolic rate was minus 1 per cent, the visual fields were normal and the urinalysis was negative. Blood chemistry studies were as follows: Non-protein nitrogen 24 mg. per cent; uric acid 2.5; cholesterol 172; phosphorus 3.95; calcium 9.6; sugar 100; the total serum proteins were 6.62 grams per cent with an albumin fraction of 4.40. She reported that she felt well and worked regularly, and that her menstrual periods were perfectly normal.

In February 1938, at the time of her last visit to the clinic, no significant changes were noted. (Table 1.) Her health had remained excellent, and she had worked

TABLE I

Measurements made during period October 1929 to February 1938. The head and chest measurements were made with a plevimeter and are expressed in centimeters.

	Oct. 1929	Feb. 1935	April 1937	Feb. 1938
<i>Head</i>				
Anterior-posterior of skull	19	20	21	20.5
Tip of chin to vertex of skull	25.5	25	26.5	26
Mastoid to mastoid	14	15	14	14
Zygoma to zygoma	14	14	13	14
Tip of chin to hair-line	20	20	20	20
Tip of nose to hair-line	12	12	11	11
Tip of nose to external occipital protuberance	23.5	24	23	23.5
Lateral angle of mandible to opposite mandible	11	11	11	11
<i>Chest</i>				
Anterior-posterior at level of xiphoid	24	22	22	21.5
Anterior-posterior at fifth costo-sternal level	26	24	25.5	25
Anterior-posterior at third costo-sternal level	25	24	24	23
Anterior-posterior at supra-sternal notch	18	18	18	17
Transverse at superior axillary levels	25	26	25	26
<i>Trunk</i>				
Height	162.6	165.1	163.2	162.6
Upper measurement		83.8	82.6	81.3
Lower measurement		81.3	80.6	81.3
Weight (kilograms)	61.4	70.7	65.9	69.1

regularly. The menstrual cycle was normal. No enlargement of the hands or feet had occurred. The blood pressure was 92 systolic, 60 diastolic. The ophthalmoscopic examination and the visual fields were normal.

DISCUSSION

When this patient was first seen there were signs both of tumor pressure and abnormal hormonal activity in association with enlargement of the hypophysis. That prompt beneficial influence was exerted by the roentgen-rays was indicated by the rapid subsidence of headache, the disappearance of evidence of pressure on the optic tracts, and the return of a normal sense of smell. The late effects were remarkable and not altogether anticipated. There was no evidence of progressive change in the skeletal system. This we had hoped for. The return of the blood sugar and basal metabolic rate to normal levels was noteworthy. The reestablishment of the menstrual cycle was more than we expected and the occurrence of pregnancy seven years after irradiation of the pituitary region was quite unpredicted.*

It is rather unusual, as judged from other reports,² to have such striking improvement occur in acromegaly after roentgen-ray treatment. It should be remembered that spontaneous remissions are known to take place.³ However, the decided improvement observed in this patient followed so soon after the roentgen-ray treatment and was in such marked contrast to the progressive downward course of the disorder up to the time of treatment that a causal relationship between treatment and improvement seems highly probable. Moreover, if a spontaneous remission had occurred in 1928 it seems likely that during the ten years which followed some evidences of hypopituitarism might have become evident. Instead there seems to have been established a satisfactory balance. It appears that overactivity of the gland ceased entirely and the functions which had been suppressed prior to roentgen-ray treatment subsequently reached and maintained a normal level of activity.

It is of interest that during the course of the pregnancy no abnormal functional activity of the pituitary was observed. The onset of acromegaly and the activation of the disorder during pregnancy have been noted.⁴

In the treatment of acromegaly uncomplicated by rapidly failing vision it may be desirable, in the light of our experience, to use deep roentgen-ray therapy in every instance whether or not signs of hypophyseal tumor are impressive. In some instances it may be then possible to avoid surgical treatment; in others, operative treatment may be delayed without detriment to the patient.

SUMMARY

A white woman, now 40 years old, developed in 1922 symptoms and signs of acromegaly. The evidence of hypophyseal tumor was impressive enough in 1928 to indicate treatment. This treatment consisted of deep roentgen-rays. The result was brilliant. Most of the symptoms were relieved and, after a childless marriage of 10 years' duration, the patient gave birth to a healthy infant in 1936. The size of the skeleton has not altered materially in 10 years.

*It is true that we do not know that her husband has had normal spermatozoa all these years, and since he refuses to cooperate with us, information relating to the present state of his spermatic fluid is not obtainable.

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BRUCELLA ENDOCARDITIS *

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BACTERIAL endocarditis due to brucella organisms is an infrequent, but serious complication, that may occur in patients with brucellosis. A review of the literature indicates that many cases have been reported as brucella endocarditis without adequate anatomical or bacteriological proof. In a recent comprehensive review of the pathology of brucellosis due to brucella of bovine origin, Albertini and Lieberherr¹ state that reports of brucella endocarditis are usually instances of brucellosis with a coincidental endocarditis present. This statement is well illustrated by the observations of Scott and Saphir.² They studied a patient who had an aortic and mitral valvulitis of rheumatic origin, but who later contracted brucellosis. *Brucella melitensis* var. *abortus* organisms were repeatedly isolated from the patient's blood. The patient exhibited the characteristics of a fatal course of bacterial endocarditis, but after a postmortem study, they concluded that it was an instance of rheumatic endocarditis associated with a brucella bacteremia.

Our interest in this subject was stimulated by the clinical and pathological studies carried out on a patient with bacterial endocarditis proved to be due to the abortus variety of brucella. We have reviewed the literature for cases of endocarditis caused by the various strains of brucella, and have found only two substantiated by bacteriological and anatomical evidence at necropsy. Casanova and D'Ignazio³ reported the first case in 1933. A 28 year old male with fever developed congestive heart failure and died. Before death, a systolic murmur was heard over the aortic area. Agglutinins for *Brucella melitensis* var. *melitensis* were demonstrated in his blood, and the organism was isolated from his blood. At autopsy, fresh vegetations were found on the aortic valve. A pure

* Received for publication July 25, 1938.

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culture of brucella recovered from the vegetations, produced the characteristic lesions of brucellosis when injected into a guinea pig. The second case is that of Rothman⁴ and concerns a 61 year old male who complained of anorexia, fever, and loss of weight. His blood serum agglutinated *Brucella melitensis* var. *melitensis* in a titer of 1 to 800. A soft systolic murmur was detected over the precordium. The patient died suddenly, and postmortem examination revealed marked destruction of the aortic valve with fresh vegetations present. The abortus strain of brucella was isolated in pure culture from the vegetation, as well as from the kidney, spleen, liver and blood. A brucella infection was established in guinea pigs with the organisms obtained from the aortic vegetations.

There are several other cases reported where precise bacteriological data obtained at necropsy are lacking, but in which there is sufficient clinical and pathological evidence to warrant a probable diagnosis of brucella endocarditis. In the reports to be cited, there are no statements that brucella were isolated from the valves at autopsy, and identified by cultural and serological methods. We may include in this group, reports in this country by de la Chapelle,⁵ and Levy and Singerman⁶ who have each presented a case of endocarditis said to be due to *Brucella melitensis* var. *melitensis*. Hardy and his associates⁷ in an excellent summary of the clinical findings in 300 cases of brucellosis occurring in Iowa included one case of endocarditis due to brucella of porcine origin. Gounella and Warter⁸ in France, described a case of vegetative endocarditis with *Brucella melitensis* var. *melitensis* as the probable cause. Rennie and Young,⁹ in England, concluded that an abortus strain of brucella was the cause of malignant endocarditis in a case studied by them.

CASE REPORT

A 29 year old white farmer residing in Minnesota entered the University Hospital complaining of weakness, loss of weight, and fever. Seven months before entry, he had a swelling of the great toe on the right foot. At the same time, he had anorexia and a cough productive of blood-tinged sputum. After remaining in bed for two weeks, he recovered sufficiently to work, but during the following two months, collapsed several times in the fields. Five months before entry, he was suspected of having hyperthyroidism because of a slight swelling of his neck in the region of the thyroid gland. His basal metabolism was found to be plus 45 per cent, and iodine solution was administered without relief of his symptoms. Three months before entry, he had chills for the first time. One month later his physician heard a systolic murmur over the apex, which had not been present on previous examinations. At this time, an agglutination test of his blood showed agglutinins present in a titer of 1 to 2,560 for *Brucella melitensis* var. *abortus*. We were informed later that 50 per cent of the cattle on the farm where he was employed showed evidence of a brucella infection. The patient had drunk raw milk obtained from these cows. One month before entry, he was given 60 to 80 grains of sulphanilamide for several days without improvement. He was then given subcutaneously on three occasions 200 c.c. of citrated blood obtained from a donor who had recovered from brucellosis. However, his condition became worse. His temperature fluctuated between 99° and 105° F. Brucella vaccine was administered subcutaneously, but he became progressively worse. Just before entry he had several episodes of nausea and vomiting.

His past history revealed no significant details. He had always been in good health until his present illness. He denied having had rheumatic fever, chorea, or a venereal disease.

Physical examination showed a well-developed, poorly nourished male, quite

prostrated. The eyes, ears, nose, and mouth showed no abnormalities. There were prominent pulsations of the neck veins. There were no abnormal findings in the lungs. The apical impulse of the heart was very prominent in the fifth interspace, 12.5 cm. to the left of the mid-sternal line. The sounds were regular, and of good quality. There was a presystolic murmur at the apex with a snapping first sound, which was followed by a loud systolic murmur. Over the aortic area a systolic murmur was heard, and a suggestive systolic thrill was felt. To the left of the sternum in the third interspace, there was a diastolic murmur. The blood pressure was 145 mm. of Hg systolic and 60 mm. diastolic. He had a water-hammer type of pulse. The abdomen was soft showing evidence of marked weight loss. The liver edge was not palpable. The spleen was firm, non-tender, and the edge was felt 3 cm. below the costal margin. No ascites was demonstrated. There was no edema of the extremities, and there were no abnormal neurological findings.

The admission diagnoses were: (1) chronic brucellosis; (2) aortic insufficiency on a rheumatic basis; (3) mitral stenosis and insufficiency, or a functional Austin Flint murmur; (4) brucella endocarditis?

Laboratory findings showed the urines to have a specific gravity of 1.010 to 1.018. Albumin and sugar were absent, and only an occasional leukocyte was present in the sediment. The hemoglobin was 58 per cent (Sahli, 17 grams per 100 c.c. = 100 per cent) on entry. There were 2,600,000 red blood cells and 2,600 white blood cells per cu. mm. The differential count showed 69 per cent polymorphonuclear neutrophils, 30 per cent lymphocytes, and 1 per cent monocytes. Thereafter, the hemoglobin level varied between 75 per cent, and 66 per cent, and the erythrocytes from 2,200,000 to 3,800,000 per cu. mm. A leukopenia was constantly present. The sedimentation rate of the erythrocytes was two mm. in two hours on entry (Westergren method); 36 mm. in two hours, one week later; and the third week after entry, 40 mm. in two hours. Wassermann, Kline, and Kahn tests done with blood serum gave negative reactions. Agglutination tests on the blood for *B. typhosus*, *B. para-typhosus* A and B, and *B. tularensis* were negative on two occasions. The Weil-Felix reaction was absent. Agglutinins for *B. abortus* were present in the blood in a dilution of 1 to 5,120 on three occasions. A culture of venous blood in veal infusion broth made soon after entry remained sterile. In culturing the blood subsequently, special media were employed. Ten c.c. of blood were added to a flask containing 100 c.c. of liver infusion broth. The flasks were placed in a closed jar containing a 10 per cent concentration of carbon dioxide. The flasks were incubated at 37.5° C. for several days, before examining them for growth. Seven blood cultures made in this manner were sterile at the end of 30 days. Two guinea pigs injected subcutaneously with the patient's blood, showed no evidence of brucellosis at the end of three weeks, and six weeks respectively.

Roentgenological examination of the chest showed cardiac enlargement of the aortic type, with no evidence of a mitral deformity. Fluoroscopic examination of the patient's heart and great vessels by Dr. Phillip Hallock revealed a small pulsation of the aorta with a left ventricular type of cardiac enlargement. These findings suggested the presence of aortic stenosis. No mitral deformity was observed.

An electrocardiogram showed left axis deviation, with slurring or notching of QRS in all four leads, which was suggestive evidence of myocardial damage.

The patient was under observation for 27 days before he died. All during this time, his temperature varied between 99° and 102° F., and was usually elevated in the afternoon. His pulse rate was between 90 and 110 beats per minute. Shortly after entry a skin test was done with the same suspension of brucella organisms used in the agglutination test by the Minnesota Department of Health. No demonstrable reaction was present in 24 and 48 hours. He was given six transfusions of citrated blood. A few days after entry, petechiae of the buccal mucous membrane were noted, and in the second week, a small hemorrhage was observed in the sclera of the right eye.

He became progressively worse exhibiting marked anorexia, weight loss, profound weakness, and severe dyspnea. From time to time, many petechiae appeared over the skin of his body. During the third week, his venous pressure in the right arm was 10.5 cm. of blood. He developed pulmonary congestion, and the liver became



FIG. 1. Vegetation aortic valve from which brucella were isolated in pure culture. Note herniation in center of vegetation.

enlarged and tender. He perspired profusely. He suddenly became apprehensive, markedly orthopneic, and expired shortly thereafter.

The postmortem examination was done four hours after death. There was slight edema of the feet and eyelids. A petechia was present in the right conjunctiva, and numerous ones over the anterior surface of the trunk and arms. The peritoneal

cavity contained about 15 c.c. of straw colored fluid. The right pleural cavity contained 200 c.c. of similar fluid, and the left 50 c.c. There were 300 c.c. of clear, yellow fluid in the pericardial cavity. There was no evidence of pleuritis or pericarditis. The heart weighed 530 grams. Numerous petechiae were noted in the visceral pericardium. The left ventricle was moderately hypertrophied and the right ventricle dilated. The mitral and pulmonary valves appeared normal. A large vegetative lesion was present on the aortic valve (figure 1). The right and posterior aortic cusps were covered by a large mass of soft friable vegetations about 2 cm. in diameter and 1 cm. in thickness. The adjacent portions of the right and posterior aortic cusps, and the aortic ring between them was eroded in such a manner that at this point there was an almost spherical outpouching or herniation 1.5 cm. in diameter. The first portion of the right coronary artery was encroached upon by this herniation. The bottom of this pocket was made up of the herniated aortic ring or upper portion of the interventricular septum, and the pocket invaded the right ventricle underneath the posterior portion of the medial cusp of the tricuspid valve. This valve leaflet was adherent to the herniation but not otherwise involved. The left and right aortic cusps were fused for a distance of about 8 mm. The root of the aorta and the coronary arteries were not sclerosed.

The right lung weighed 650 grams, and the left 615 grams. Cut sections of both lungs were of a uniform, rusty brown color, and somewhat doughy in consistency. There was evidence of slight edema, but no consolidation. The spleen weighed 1100 grams. On section it was of uniform red color and of soft consistency. There were no infarcts. The liver weighed 3900 grams. The surface was smooth. Cut section revealed it to be soft, pale, swollen, with a marked nutmeg appearance. The gastrointestinal tract was normal except for some congestion of the mucosa. The pancreas and adrenals appeared normal. The right kidney weighed 290 grams, and the left 310 grams. The surfaces were smooth. On section, they were swollen, congested, and cloudy. There were a few petechiae in the pelvis. Permission was not obtained for examination of the brain.

Microscopic examination of the organs showed none of the tubercle-like epithelioid cell structures which have been described in many cases of brucellosis. The heart showed a focal myocarditis of moderate intensity. The cellular accumulations were small and composed mainly of small mononuclear cells. A section of the left aortic cusp not involved by the vegetations showed no definite evidence of an older inflammatory process, but there was a slight acute inflammatory reaction just under the surface. The right and posterior aortic cusps where they were involved by vegetations revealed a marked destruction of the valve tissue by a chronic inflammatory process. The vegetations consisted mainly of platelets and fibrin with a thin zone of lymphocytes at the periphery. There was much calcification present. There were large clumps of small coccoid organisms throughout the vegetations. The masses of bacteria in the vegetations appeared blue when stained by the Gram-Weigert method, even though brucella are gram negative organisms. This discrepancy will be commented upon shortly. The lungs presented the picture of atelectasis, emphysema, and chronic congestion. The liver sections showed moderate central necrosis, and the changes of passive congestion. The spleen showed no fibrosis but there was a cellular infiltration consisting of numerous macrophages, and small numbers of plasma cells and polymorphonuclear leukocytes in the pulp. The glomeruli of the kidneys exhibited a slight degree of endothelial proliferation. There were small foci of chronic inflammatory exudate throughout the interstitial tissue. In the periaortic lymph nodes there was a marked degree of hyperplasia of the sinus reticulum with beginning fibrosis. The sinuses contained numerous macrophages, and a finely granular brown pigment was noted in the reticular cells.

Postmortem Bacteriological Studies. Microscopic examination of a smear of the vegetation on the aortic valve stained by Gram's method revealed myriads of small,

cocco-bacillary, gram negative organisms having the morphological appearance of brucella. No other organisms were present. Material was cultured in liver-infusion broth from the aortic vegetation, kidney, spleen, heart's blood, lung, periaortic lymph node, pericardial fluid, bone marrow and liver. Pure cultures of *Brucella melitensis* var. *abortus* were obtained in this manner from the vegetation, kidney, spleen, heart's blood, and lung. Growth took place only in a jar having an increased carbon dioxide tension. The isolated organisms were agglutinated by brucella antiserum of the abortus type in a dilution of 1 to 2,560. Guinea pigs were inoculated with the cultures obtained from the heart's blood. When autopsied four weeks later, *Brucella melitensis* var. *abortus* was identified in pure culture from the animals' spleen.*

The anatomical diagnoses were: Brucella endocarditis with bacteremia; chronic splenitis; chronic congestion of the lungs and liver; focal myocarditis; chronic lymphadenitis.

DISCUSSION

There are several features of this patient's illness that merit further discussion. To recapitulate, he had a sudden departure from health with weakness, fever, and loss of weight as the outstanding symptoms. In addition, he developed chills and episodes of profuse perspiration. Agglutinins were present in the blood in a high titer for brucella organisms. No cardiac abnormality was found when he first consulted a physician. The signs of a progressive valvulitis appeared, and death was due to cardiac insufficiency. The chronological development of these signs and symptoms, with sufficient laboratory data, warranted a diagnosis of chronic brucellosis, and acute endocarditis. The appearance of embolic phenomena in the form of petechiae suggested a bacteremia, and the presence of a bacterial endocarditis.

It is significant that repeated blood cultures remained sterile. Huddleson¹⁰ has emphasized the difficulties encountered in culturing brucella from the blood. Special media must be employed, and brucella of the abortus variety appear to grow only in an atmosphere of increased carbon dioxide tension. We utilized Huddleson's technic and yet were unsuccessful in isolating organisms. The injection of the patient's blood into animals yielded negative results. That the patient had a bacteremia at some time is proved by the recovery of brucella from various organs at autopsy. Keefer¹¹ has recently called attention to those cases of bacterial endocarditis without bacteremia. He points out, with sufficient immunological data, that the blood may be rendered free of bacteria because of a high degree of immunity that develops, and that the bacteria are localized on the heart valves. However, embolic phenomena indicate bacteria are present in the blood at times. In the present case, immune bodies in considerable quantity were present in the blood as shown by the high agglutinin titer (1:5,120).

The skin test has been considered a useful adjunct by Huddleson¹⁰ and others¹² in the diagnosis of brucellosis. The usual procedure is to inject killed brucella organisms intradermally, and note any reaction 48 hours later at the site of the injection. A positive test consists of edema, redness and perhaps some pain over this area. We have used the skin test as an aid in the diagnosis of this disease, and reactions have been obtained in all patients with active

* We are indebted to Dr. O. McDaniel, Director of the Minnesota Department of Health, Division of Preventable Diseases, for cooperating with us in the study of this patient, and to Dr. L. S. Heathman and Miss M. MacLanahan for assistance in the isolation and identification of the organism.

brucellosis, except in the present case. Although several skin tests were done on the patient, at no time was there a positive reaction. It is of interest that although his blood agglutinated a suspension of brucella organisms in a titer of 1:5,120, when the same suspension in varying dilutions was injected into his skin, there was no reaction noted. It has been observed^{11, 13, 14, 15} that negative skin reactions occur in patients with subacute bacterial endocarditis due to streptococci of the viridans type when the filtrates of protein extracts of streptococci are injected intradermally. This absence of skin activity may be a useful aid in the diagnosis of obscure cases of subacute bacterial endocarditis.

We should like to point out the inadvisability of using the Gram-Weigert stain in differentiating gram negative and gram positive organisms in tissue preparations. We utilized this technic in studying sections of the vegetations from the aortic valve, and the organisms were stained a deep blue color. The organisms appeared to have the same morphological characteristics as *Streptococcus viridans*. Thus the histological appearance was the same as that seen in vegetative endocarditis due to the *Streptococcus viridans*. Smears from the vegetation stained by Gram's method showed gram negative cocco-bacilli. It was only by obtaining brucella organisms in pure culture from the vegetation that the true nature of the lesion was ascertained. Others^{16, 17, 18} have pointed out the discrepancies that result in the use of the Gram-Weigert stain, and have proposed more exact methods of study.

It is of interest that in the case cited a brucella infection was apparently superimposed upon a previously normal aortic valve. No cardiac murmurs were heard when the patient first became ill. Histological examination of that part of the valve not involved by vegetation, did not give evidence of an underlying chronic valvulitis. In subacute bacterial endocarditis it is not unusual for bacteria to localize on previously normal valves.¹¹

SUMMARY AND CONCLUSIONS

1. Brucella endocarditis is an infrequent complication arising in patients with brucellosis. It may be caused by any one of the three varieties of *Brucella melitensis*.

2. The literature is reviewed, and the clinical and pathological findings of a fatal case of brucella endocarditis due to brucella of the abortus variety are presented and discussed.

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BERI-BERI; SEVERE MANIFESTATIONS OF BOTH THE 'WET' AND 'DRY' FORMS IN THE SAME PATIENT; RECOVERY FOLLOWING TREATMENT *

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THE cardiovascular complications of inadequate vitamin consumption have been traced to vitamin B₁ deficiency. The specificity and cure of the cardiac manifestations of this avitaminosis recently were reaffirmed by Hashimoto,¹ who reported a case in which dramatic recovery followed the intravenous administration of minute quantities of purified and concentrated vitamin B₁.

The condition may manifest itself in a 'dry' type, characterized by muscle wasting and peripheral neuritis, or a 'wet' type in which generalized edema and cardiovascular disturbances predominate. The combination of an acute form of one type with a mild form of the other is uncommon, and likewise the presence of a severe form of both types in the same individual is rare.²

A low standard of living, derangements of pregnancy resulting in poor food intake or utilization and chronic alcoholism are instances in which the outstanding factor is the inability or reluctance of the patient to obtain or to utilize a diet adequate in vitamin requirements.

* Received for publication August 3, 1938.

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We are reporting a case in which all the signs and symptoms of both the 'wet' and 'dry' forms of B₁ avitaminosis appeared after a young asthmatic woman, allergic to many foods, curtailed her diet drastically in an effort to obtain relief.

CASE REPORT

B. N., a 25 year old factory worker, first developed sinusitis at the age of 14. Asthmatic symptoms which were relieved by adrenalin appeared one year later. At the age of 18 she was confined to bed for eight weeks because of bronchopneumonia. The symptoms of sinusitis and asthma became more severe, failing to respond to sinus irrigations, removal of nasal polyps and other measures.

The patient was given cutaneous tests and found sensitive to rye, tomato, barley, cheese, cauliflower, all grain cereals, fish, coffee and banana. Elimination of all possible offending substances to the point of starvation failed to ameliorate her asthmatic seizures.

During January 1936, a course of injections of autogenous vaccine was started. Following the first injection, she complained of nausea, vomiting and exacerbation of her asthmatic symptoms, and the series was discontinued.

Diarrhea lasting five days followed. Neither blood nor mucus was present in her stool. The gastrointestinal discomfort was continuous until April 1936, at which time she became bedridden. Asthenia and anorexia became progressively worse. During this entire time she continued to restrict her diet rigidly. Nevertheless, the asthmatic seizures became more frequent.

During June 1936, she noted pain, weakness and stiffness of both hands and feet. The pain, which initially was worse at night, soon became almost continuous. Paresthesias appeared in both the upper and lower extremities.

Pitting edema of the lower and upper extremities then was noted. Radiographic examination of the chest on June 11, 1936, was negative. Another roentgenogram of the chest taken on July 23, 1936, revealed the presence of bilateral hydrothorax and an increase in the frontal silhouette of the heart. Physical examination of the heart at that time gave no positive diagnostic findings. There were no subjective symptoms which might have been attributed to circulatory failure.

Several leukocyte counts during June and July 1936, showed a leukocytosis varying from 10,000 to 30,000, with an eosinophilia varying from 30 per cent to 70 per cent.

A biopsy taken from the deltoid muscle revealed no evidence of trichinosis. The vascular structures were normal. Repeated examinations of the urine proved negative.

The patient was seen again in March 1937. At that time there was pronounced shortness of breath. The burning and tingling sensations in her extremities had become constant, and were extremely painful. Small black spots had appeared on the toes of both feet and the distal phalanges of both hands during February 1937. Within a month they coalesced and developed into dry gangrene (figure 1a). Oscilometric readings made on March 17, 1937, showed marked diminution in the circulatory beds of all four extremities.

On March 4, 1937, pretibial edema reappeared. Radiographic examination of the chest revealed fluid in both pleural cavities and an increase in the size of the heart shadow. An electrocardiogram taken on April 1, 1937, revealed regular sinus rhythm. The ventricular rate was 110. The 'S'-wave in Lead I was prominent. There was a tendency towards right axis deviation. The p-R interval was 0.18 second.

The degree of the edema progressed rapidly, so that by the end of April 1937, anasarca was present. The serum albumin was 2.1 per cent, serum globulin 2.6 per cent. She was given several mercurial diuretic injections which resulted in excellent



FIG. 1a. Gangrene of finger tips before vitamin therapy.
FIG. 1b. The gangrene of the finger tips has healed almost completely, after vitamin therapy.

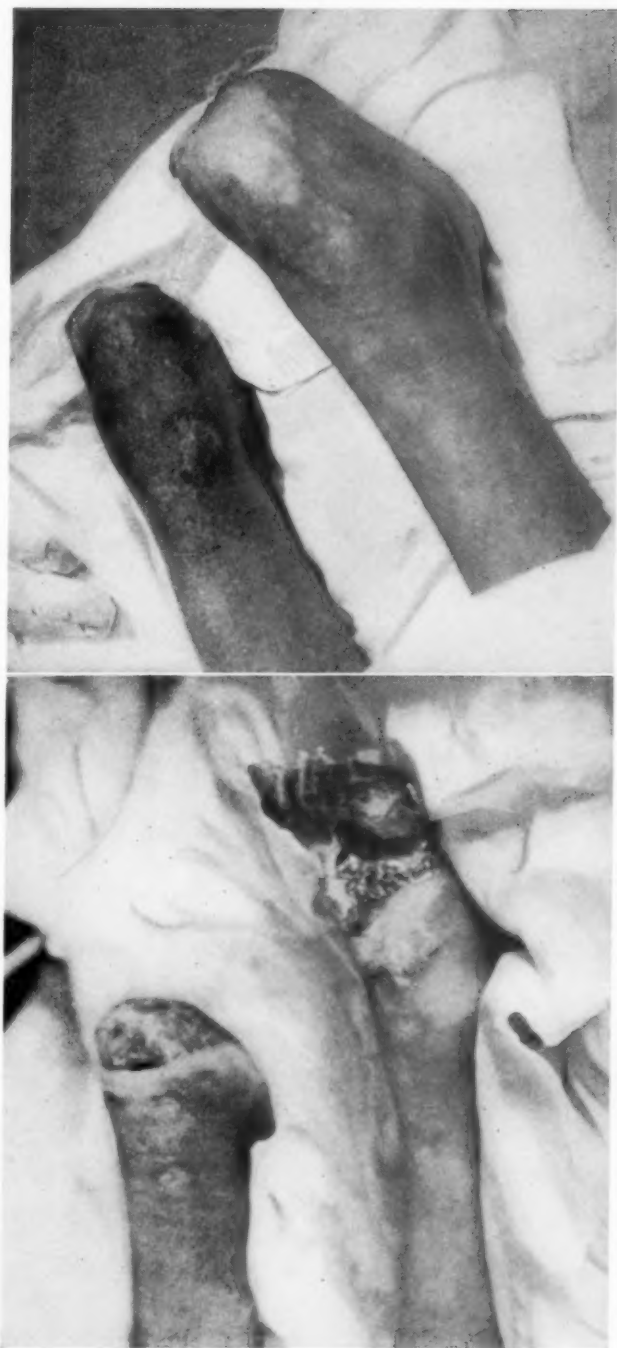


FIG. 2a. Spontaneous amputation of the left foot, unhealed. Gangrene of distal half of the right foot.
FIG. 2b. After surgical revision of right foot and vitamin therapy.

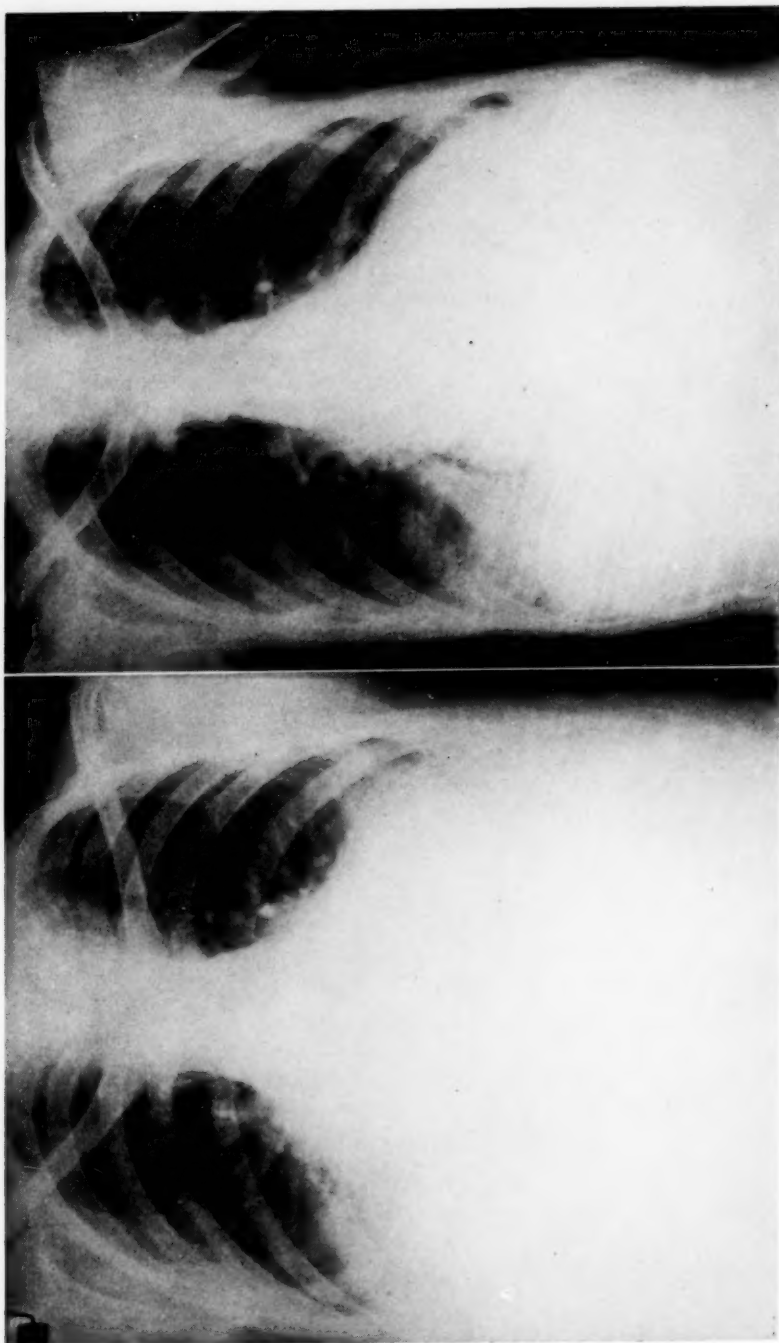


FIG. 3a. Teleoroentgenogram taken May 17, 1937, showing bilateral hydrothorax and increase in the size of the heart shadow.
FIG. 3b. Teleoroentgenogram taken June 12, 1937, following mercurial diuretics and an adequate diet. The lung shadows are clearer, but some fluid persists in the costophrenic sinuses. The heart shadow is smaller.

diuresis but in little decrease of the edema. Dyspnea, however, became less pronounced, and the patient was somewhat more comfortable.

On April 26, 1937, a spontaneous amputation of the distal third of the left foot occurred while the patient was in bed (figure 2a). The tissue proximal to the site of amputation showed evidences of satisfactory circulation. Examination of the specimen revealed nothing of diagnostic value.

She remained alert and coöperative, but still refused food. On physical examination during May 1937, the deep and superficial reflexes were found equal and active. No pathologic reflexes could be elicited. The heart rate was 80 per minute. The heart sounds were of poor quality, and no murmurs were audible. There were signs of fluid in both pleural cavities, confirmed by radiographic examination (figure 4a). Pitting edema up to the waist was so pronounced that a definite line of demarcation could be seen separating the edematous lower half of her body from the wasted upper half. Her blood pressure was 140 mm. of mercury systolic and 100 mm. diastolic.

Both upper extremities were markedly atrophied, cold and cyanotic. The terminal phalanges of both hands and the distal phalanges of the right foot were shrivelled and black, presenting the picture of dry gangrene. Necrotic bone protruded from the site of the spontaneous amputation. A surgical revision of the amputation stump of the left foot and amputation of the toes of the right foot were performed.

Histologic examination of tissue taken from the left gastrocnemius muscle at this time revealed normal vascular structures. Blood counts showed a leukocytosis varying from 11,500 to 18,000. The highest eosinophile count was 8 per cent. On several occasions no eosinophiles could be seen in the blood smears.

The serum proteins remained low, the albumin being 2.1 per cent and the globulin 2.6 per cent. Her weight was 86 pounds, a loss of 40 pounds since the onset of her illness.

Examinations of the urine showed the presence of albumin varying in amount from one to four plus. The blood urea nitrogen never exceeded 25 mg. per cent. The blood chlorides were 450 mg. per cent, and the cholesterol was 160 mg. per cent. The basal metabolic rate was minus 11.

Repeated mercurial diuretics administered intravenously and by rectal suppositories were very effective.

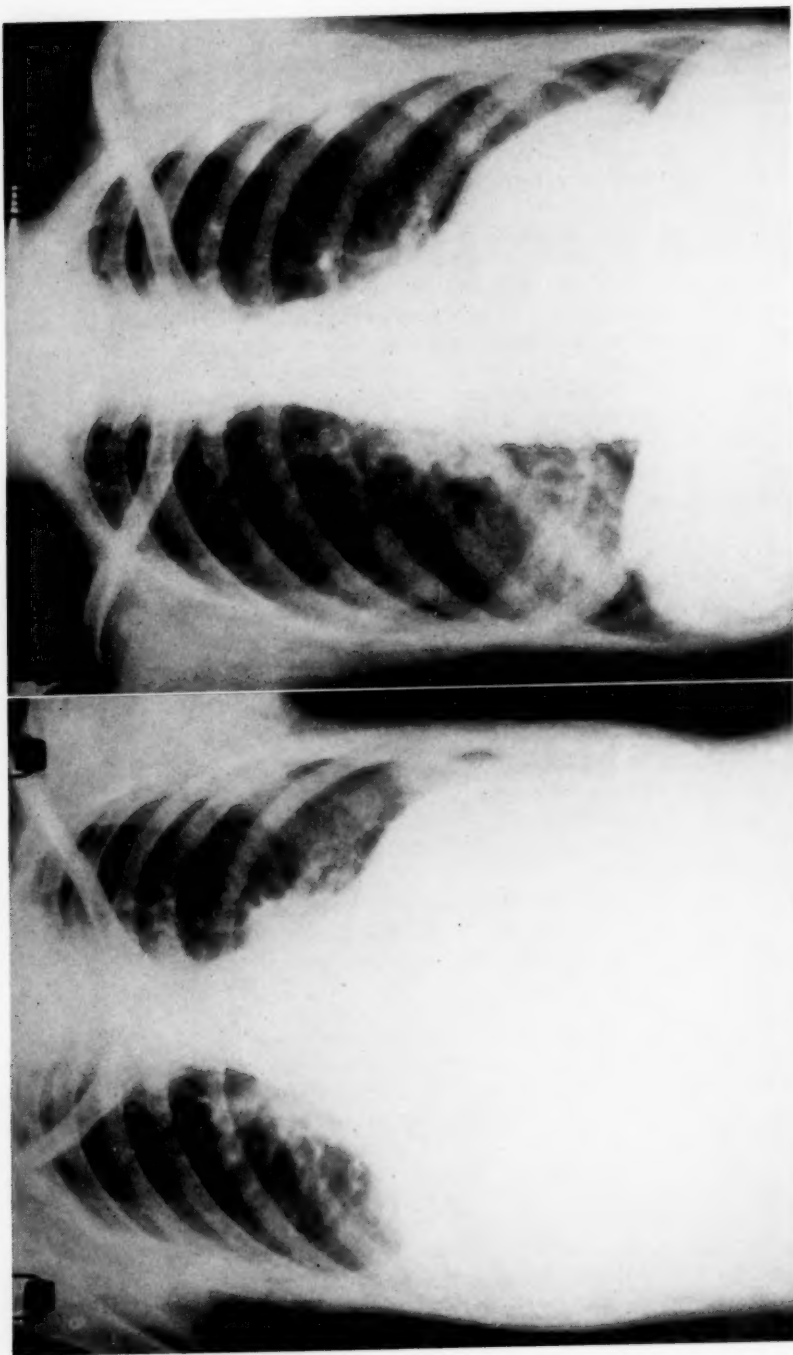
During the latter part of May 1937, the patient was encouraged to increase her diet, which was fortified with capsules of vitamin B concentrate.* At first she was recalcitrant, but after a few days of encouragement she began to take a fairly ample diet.

Improvement followed rapidly. The mercurial diuretics became even more effective than heretofore. Radiographic examination of the chest on June 12, 1937, showed the pleural cavities to be practically free from fluid (figure 4b).

During the next month difficulty again was encountered because she refused both her food and medication. A chest radiogram taken on July 23, 1937, showed re-accumulation of fluid in both pleural cavities (figure 4a). Further mercurial diuretics together with an increased diet and vitamin concentrates taken regularly again resulted in definite, and this time, lasting improvement. The chest fluid and peripheral edema vanished, and neither has recurred since.

During the next four months the patient made continual progress. The signs and symptoms of cardiovascular insufficiency disappeared, and the cardiac silhouette reassumed a normal configuration (figure 4b).

*The vitamin was first administered in the form of capsules containing vitamins A, B and D. Tablets of thiamin chloride, containing 1 mg. of thiamin chloride were added after the first week. The average daily dose during the first six weeks of treatment was equivalent to eight to ten milligrams of thiamin chloride daily in addition to a diet planned to contain a high amount of natural vitamin B.



4a

4b

FIG. 4a. Teleoroentgenogram taken July 23, 1937. The pleural effusion has recurred after the patient refused her diet.
FIG. 4b. Teleoroentgenogram taken September 3, 1937, after the patient had been on an ample diet fortified with vitamin B-1. The lung fields are clear, and the heart shadow is smaller. Some residual infiltration is seen at the right base.

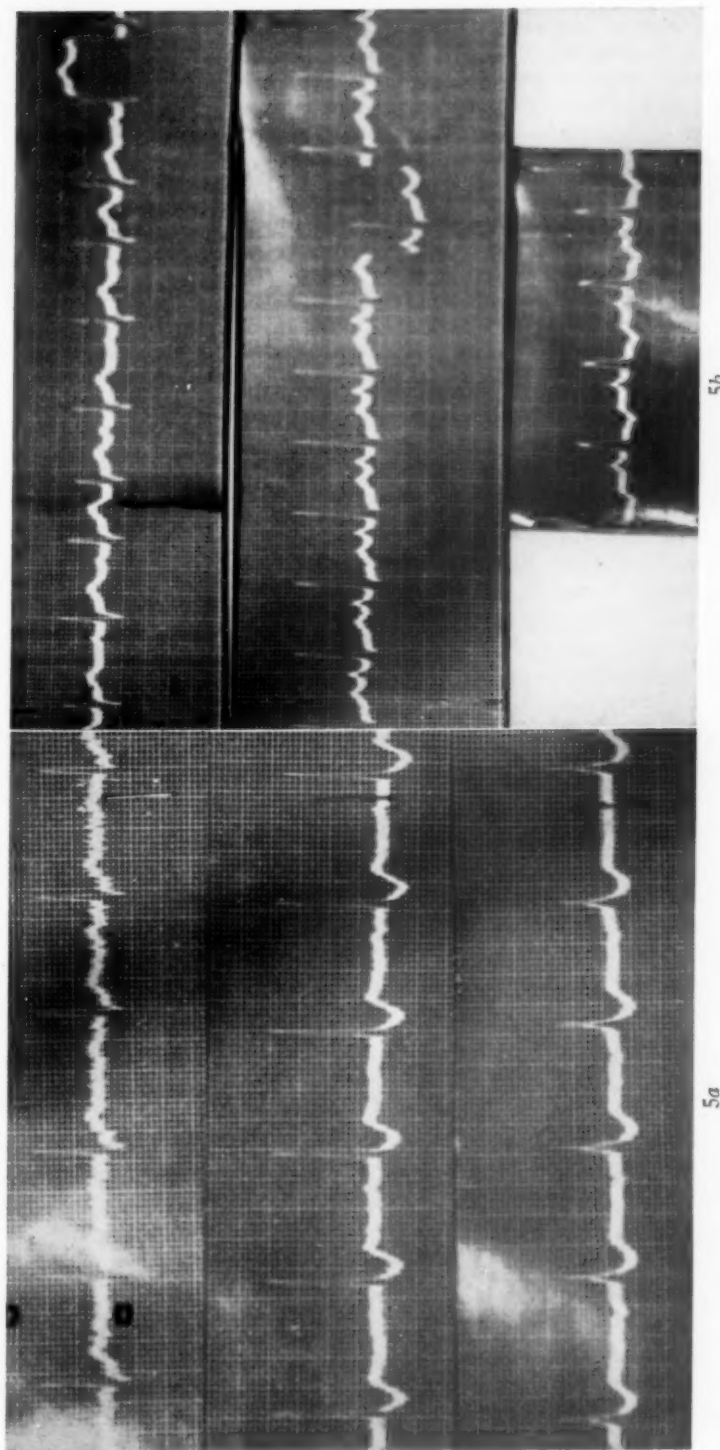


FIG. 5a. Electrocardiogram taken October 3, 1937. Note inversion of the "T"-waves in Leads II and III.
FIG. 5b. Electrocardiogram taken June 2, 1938. The "T"-waves in Leads I and II are erect. An occasional auricular extrasystole is present in Lead I.

An electrocardiogram (figure 5a) taken on October 3, 1937, showed regular sinus rhythm. The P-R interval was 0.24 second. The T-waves in Leads II and III were inverted, and the R-T take-off was abrupt and low. A subsequent electrocardiogram taken on June 2, 1938 (figure 5b) showed occasional auricular extrasystoles. The P-R interval was 0.18 second. The T-waves in Leads I and II were erect, and inverted in Lead III. The R-T take-off was normal.

The painful sensations in the extremities gradually diminished, and the gangrenous finger tips began to show signs of renewed vitality. At present there is definite wasting of the soft tissues of the ungual extremities of both hands and loss of finger tactile sensibilities (figures 1b). The stumps of both feet have a definitely pink, healthy appearance, and are not painful (figure 2b). All four extremities have recovered their normal contour and texture.

Asthmatic symptoms still are present, but are controlled more easily with adrenalin. The patient is cheerful, and partakes in occupational therapy work. She has gained considerable weight.

COMMENT

This patient is one in whom the manifestations of both the "dry" and "wet" forms of beri-beri appeared at about the same time, and over the period of a year advanced to unusually severe forms. The prolonged clinical course and the apparent cure may be taken as an indication that even far-advanced cases may respond well to treatment.

The relationship between the dietary restrictions and ensuing avitaminosis is apparent. It seems that severe elimination diets because of food sensitivities may be added to the list of possible causes of hypovitaminosis.

The gangrene of the fingers and toes progressing as far as spontaneous amputation is unusual. The small black spots which appeared first on the fingertips and toes in all probability were foci of local gangrene. In spite of the negative findings in the blood vessels of the muscle biopsied the presence of a generalized vascular abnormality of a spastic nature must be postulated. This is borne out by the oscillometric readings made during the height of the disease, and the return of normal color and moisture of the extremities after therapy had been instituted.

Cardio-respiratory symptoms did not appear until the patient had been ill for nine months. Hydrothorax and pericardial effusion, however, had been present from the third month of her illness. Mercurial diuretics were effective during the period of avitaminosis, but their potency was augmented considerably by adequate diet and vitamin concentrates. The reversability of the electrocardiographic and radiographic findings is worthy of mention.

The tremendous edema no doubt had a nutritional as well as an avitaminotic factor. Repeated examinations of the blood serum proteins showed hypoproteinemia during the course of the disease, with a prompt rise after therapy had been administered.

Exercise as a factor in the development of heart failure is ruled out inasmuch as the patient was bedridden before the subjective symptoms of heart failure appeared.

The marked eosinophilia noted during June and July 1936 probably was on an allergic basis rather than related to the avitaminosis. The eosinophilia disappeared later, while the manifestations of beri-beri continued.

SUMMARY

An asthmatic patient is reported, in whom severe manifestations of both the "wet" and "dry" forms of beri-beri appeared after restriction of diet.

Recovery followed increase in diet and addition of vitamin B concentrates.

REFERENCES

1. HASHIMOTO, H.: Acute pernicious form of beri-beri and its treatment by intravenous administration of vitamin B-1, *Am. Heart Jr.*, 1937, xiii, 580-588.
2. WEISS, S., and WILKINS, R. W.: Disturbances of the cardiovascular system in nutritional deficiency, *Jr. Am. Med. Assoc.*, 1937, cix, 786-793.

EDITORIALS

SMALLPOX

Public Health Reports ¹ draws our attention to the astonishing prevalence of smallpox in the United States. In 1937 this country led all other nations of the world, except India, in the number of smallpox cases reported. The number occurring in the United States that year was 11,673. In 1938 an increase was noted to approximately 15,000.

These figures are the more humiliating when we learn that in 1936 England and Wales, with a population of 40,839,000, reported only 12 cases; France, with 41,906,000 population, reported 273 cases; and Germany, with a population of 67,346,000, reported no cases.

The record of the various states as to smallpox incidence is very uneven. The mountain area of the west showed the highest incidence in 1938, 38.4 cases per 100,000 population. The west north-central and Pacific areas likewise showed incidences above 30 per 100,000. In the other central areas the incidence averaged close to 11 per 100,000. On the other hand the states along the Atlantic coast are practically free from smallpox. In 1938 the New England and middle Atlantic areas did not report a single case and in the south Atlantic area the incidence was 0.6 per 100,000.

Recently, in a Statistical Bulletin of the Metropolitan Life Insurance Company, it was stated that New Jersey, with a population of about 4,400,000, has not had a case of smallpox for more than seven years, while the states of North Dakota, South Dakota, Montana, Idaho, Oregon, Wyoming and Utah, with a combined population less than that of New Jersey, reported during the same period a total of more than 12,000 cases.

The eastern seaboard suffered such ravages from virulent smallpox in Colonial days and in the last century, and moreover had so many and such convincing demonstrations of the efficacy of vaccination, that compulsory vaccination is universally prescribed and well enforced. The same is not true in the afflicted area.

For the last 20 years, it is true, the type of smallpox seen has for the most part been mild with a very low mortality. Older physicians, however, well remember the day when the mortality in unprotected cases ranged between 25 and 35 per cent. That virulent forms can still occur was demonstrated in the Minneapolis epidemic in 1924 when 993 cases occurred with 221 deaths. There is no sound basis for a belief that smallpox will permanently retain its present mild form.

Should a virulent type of smallpox be imported or develop locally its ravages will be limited to the unprotected population. Those communities which allow a large part of their population to go unvaccinated will suffer severely. It is surely the continuing duty of all physicians to urge the passage of compulsory vaccination bills before such calamities have occurred.

¹ Why smallpox?, Public Health Rep., 1939, liv, 1091-1093.

THE SPREAD OF ROCKY MOUNTAIN SPOTTED FEVER

The gradual spread of Rocky Mountain Spotted Fever into new areas of the country is attracting the attention of both public health officials and of practising physicians. The number of cases is nowhere very great but the severity of the disease and its relatively high mortality in certain regions have given rise to a considerable degree of apprehension on the part of the public. The presence of ticks, known to be capable of transmitting the disease, in the underbrush of recreational areas has naturally led to some anxiety among those planning vacations. In foci where numerous cases have occurred depreciation in land values results.

The disease was first known to the medical profession as a highly fatal fever, accompanied by a generalized, often hemorrhagic, eruption, occurring in the western part of Montana and especially in the Bitter Root Valley. It is now known to be one of a world wide group of diseases due to the *rickettsiae*. The present conception is that it is primarily a disease of the native fauna and that it is carried from animal to animal by the bite of ticks and fortuitously from animal to man by the bite of such ticks as have the characteristic of feeding upon both the infected animal species and man. In addition the disease agent may survive for long periods in the body of the tick; it may be transmitted from tick to tick during copulation; and from the female tick through the egg to the larva.

Of the ticks which fasten readily upon man two have been proved to be of chief importance in carrying the disease: *Dermacentor andersoni* (the Rocky Mountain wood tick) whose range is roughly from the west-central states to the Pacific coast with maximum concentration in the Rocky Mountain region; and *Dermacentor variabilis* (the American dog tick) which is distributed generally, though in varying frequency, from the Atlantic coast to the Rocky Mountains.

Prior to 1930, reports of the disease were practically confined to states lying west of the east-central group but since that time an increasing number of cases has developed in the eastern half of the country. In this new area the greatest number of cases has been reported from the states of Maryland and Virginia and from the District of Columbia, and the fewest from the New England states. The relative scarcity of the *Dermacentor variabilis* in the New England group of states may explain the infrequency of the disease in this region.

The seasonal incidence of the disease corresponds both in the East and West with the seasonal period of activity of the two tick species chiefly involved in transmission. Since at this time the tick season for 1939 is practically over in both areas it is possible from the reported cases to form some estimate concerning the present relative frequency of Rocky Mountain Spotted Fever in different parts of the United States. In a recent number of Public Health Reports¹ the cases reported from February 26 to September 9,

¹ Prevalence of disease. United States: Rocky Mountain Spotted Fever, Public Health Reports, 1939, liv, 1699.

1939, are given by states. Cases have been reported from 25 states. The total is 485.

Of these reporting states 10 are eastern states, extending from New York to Georgia. The total of reported cases in this group of states is 218. The largest number of cases in any state was in Maryland where 66 cases were reported. This number incidentally was the highest for any state in the union.

From the central states cases have been reported from seven states totaling 99. Iowa reported the highest number, 27, for any state in this group.

Of the entire western group of states only eight reported cases, the total being 168. Wyoming reported the largest number of cases, 43. From Montana, the original home of the disease, only 22 cases were reported.

It is evident that not only has Rocky Mountain Spotted Fever greatly extended its range in the last decennium but that at the present time more cases are occurring in the eastern section of the country than in the Rocky Mountain region. Indeed, in Maryland, the District of Columbia, Virginia and North Carolina alone, a total of 160 cases was reported, which is very close to one-third of the total for the whole country.

Such an outcome was predicted when the disease was first recognized in the East, on the basis of the greater density of population in the eastern states and the apparent abundance both of susceptible fauna to serve as a reservoir and of ticks capable of transmitting the disease.

Our knowledge of the cycles of incidence of this disease and of all the factors involved in its perpetuation and transmission is as yet quite insufficient to warrant prediction as to the future part it may play as a public health problem. It is encouraging, meanwhile, to know that improvements in vaccine production for the rickettsial diseases are being rapidly attained.

REVIEWS

Handbook of Hematology. In 4 volumes. Edited by HAL DOWNEY, Professor of Anatomy, Medical School, University of Minnesota, Minneapolis. Thirty-seven contributors. 3136 pages. 1448 illustrations, including 50 colored plates. Paul B. Hoeber, Inc. (Medical Book Department of Harper Brothers), New York. 1938. Price, \$85.00 set. Volume two—pages 699–1586.

Volume two of the *Handbook of Hematology* presents, in nine sections, further discussions of some fundamental aspects of the morphology and physiology of the hematopoietic system. The topics included range from a presentation of data concerning blood studies in representative species of the animal kingdom, to a consideration of the work done with tissue cultures of blood cells and blood-forming organs. In all chapters the information is presented in scholarly fashion and is supplemented by a plentitude of illustrations which are excellent throughout.

Beginning with a section devoted to comparative hematology, there are succeeding chapters covering particular parts of the hematopoietic system. Thus, in separate sections are discussed the embryogenesis of mammalian blood, macrophages, fibroblasts, lymphatic tissue, the reticulo-endothelial system, and the von Kupffer cells of the liver. The discussion of these topics by individual contributors has resulted in a repetition of similar material in some places. In all sections the data appear to lend strong support to the monophyletic theory of blood cell origin. Jordan, in the section on comparative hematology, notes that even in the invertebrates the stem cell is a lymphocyte-like element of mesenchymal origin which has the general characteristics of the mammalian small lymphocyte. The inter-relationship of cells of the connective tissues with blood cells is noted in several sections. Fundamental questions as to the development potencies of these cells are discussed. The classical contributions of Maximow to this subject are frequently utilized in the four sections contributed by William Bloom. These data, although presented in a lucid, often brilliant manner, do not entirely clear the air of the various contradictory theories of blood-cell origin. The results of tissue cultures of these cells have as yet been of only minor significance. Many fundamental questions, including Maximow's observations on the transformation of lymphocytes into granulocytes, remain to be solved perhaps by the introduction of newer technical methods in this difficult field.

The largest section in this volume is that devoted to a detailed exposition of the reticulo-endothelial system. In aiming for completeness the author, R. H. Jaffe, has included many data which are probably more of historical interest than of practical value. There is, moreover, considerable space given to discussion of the part played by these cells in disease entities not directly of hematological interest. The wisdom of the inclusion of this material is somewhat doubtful.

Of more interest to the clinician is the section devoted to discussion of the normal blood values in infants and children and also that on monocytic leukemia. The former will undoubtedly serve as a constant source of reference for the pediatrician as well as the clinical hematologist. The chapter on monocytic leukemia is in reality a critique of all the available clinical material with reference to the existence of this entity as a distinct variety of leukosis. Downey is of the opinion that there exist two hematological varieties of monocytic leukemia which are designated respectively as the Schilling and Naegeli types. In the former, widespread proliferation of the R-E system is found at autopsy, whereas, in the latter, the formation of monocytes from myeloblasts can be observed. The former must be differentiated with care from those conditions known to produce systemic proliferation of the system of histocytes.

The accumulation of the material in this volume represents a task for the accomplishment of which the editor, publisher, and individual authors are due the appreciation of all interested in hematology.

M. S. S.

The Mechanism of Thought, Imagery, and Hallucination. By JOSHUA ROSETT, M.D. 289 pages; 26 × 18 cm. Columbia University Press, New York City. 1939. Price, \$3.00.

This book is an investigation into the neuro-physiological basis of the mechanism of thought, imagery, and hallucination. The style in which the book is written is unusually lucid and the clarity of exposition is not a little heightened by the frequent use of strikingly apt analogies and comparison.

The book is divided into two parts: one—fundamentals, and two—the mechanisms. Following an introduction that serves as a brief survey of the problem of consciousness as dealt with by philosophers, the author devotes a chapter to the description of Hughling Jackson's law of evolution and dissolution of the nervous system and its application to different phases of the conscious state. There are two important and exceedingly clear chapters on the physical basis of the emotions and on the autonomic nervous system and its relation with every bodily activity. The first portion of the book is closed by a chapter on representation and symbolism that is both informative and entertaining because of the use of a dry humor in the choice of illustrative examples. The second part of the book deals with the phenomena of thought, imagery, and hallucination and their mechanism as evidenced in the sequelae of injuries of the sensory receptive areas of the cerebrum, in the epileptic seizure, in the state of attention, and in sleep. Each chapter is followed by an excellent summary and well-selected references.

Psychological medicine has long been seeking for an adequate biological explanation of mental phenomena and Dr. Rosett has not only indicated the direction of further investigation but has made a definite contribution in this field. This is a stimulating and thought provoking book and should be of interest to physicians in general, as well as to neurologists and psychiatrists.

B. F. V.

The Emotional Factor in Visceral Disease. By H. G. MCGREGOR, M.D., M.R.C.P. 198 pages; 22.5 × 14 cm. Oxford University Press, London. Humphrey Milford. 1938. Price, \$3.00.

After a brief introduction by Dr. R. D. Gillespie, Dr. McGregor's book is divided into an excellent study of the various theories of emotion and its effect on physiologic function, followed by sections on the digestive system, respiratory system, cardiovascular system, and "the emotion-reaction mechanisms." In each of these sections the author reviews experimental work and what is known of normal changes in physiology both in man and animals under various emotional stresses; then takes up specific disorders. In the digestive system, for instance, he pays particular attention to peptic ulcer, ulcerative colitis, bloody diarrhea, and mucous colitis; in the respiratory system to asthma; in the cardiovascular system to "soldiers' heart" and blood pressure changes. All the way through he offers suggestive evidence that in many cases these disease pictures are primarily the result of emotional factors, illustrating these assertions with cases which are suggestive but by no means prove the point.

There is a rather misleading tendency at times to attribute specific pictures to specific cause. He suggests, for example, that gastric ulcer is the result of fear; colitis the result of immaturity; asthma the product of a certain type of personality. We doubt that any such specific constellations can be demonstrated and feel that many of the conclusions drawn are too far reaching.

The case histories are exceedingly brief. This may account for the fact that they seem rather misleading at times.

Throughout the book there are many excellent observations. The sections on the endocrines and the autonomic nervous system are stimulating. Treatment as suggested sometimes seems too simple and too satisfactory to be true, but ways are suggested in which every practitioner can be helpful to the type of patient who is apt to be passed over.

Dr. McGregor does not advocate protracted or extended methods and reminds us that deep and prolonged treatment is frequently unnecessary. The book is well written and very readable. Inasmuch as it presents a point of view too easily neglected, we feel that it is provocative enough to be an addition to one's library.

H. M. M.

Principles and Practice of Ophthalmic Surgery. By EDMUND B. SPAETH, M.D. 835 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1939. Price, \$10.00.

The first chapter of this volume deals with anesthesia, preparation of patient, and instruments to be used. Following this are chapters on general pathology of the orbit, its surgical treatment, and plastic repair of deformities; surgery of the lacrymal apparatus; enucleation and allied operations; surgery of the ocular muscles, and its indications. There are two chapters on plastic surgery and five on surgical conditions of the lids. A chapter on the anatomical factors connected with surgical procedures on the eyeball precedes a description of the surgery of the conjunctiva, sclera, cornea and iris. General considerations connected with cataract surgery, the technic of cataract operations, indications and contra-indications for various procedures, and their complications are discussed in detail. Glaucoma and retinal detachment are as completely considered. The last chapter deals with trauma of the globe, localization of foreign bodies and their removal, radium and roentgen-ray therapy, glioma retinae and plastic repair of tumor sites.

In this very comprehensive work on ophthalmic surgery practically all worth-while operations are described in detail and where necessary are illustrated.

The author is to be congratulated on this volume which fills a much needed place in the American literature on ophthalmology.

H. F. G.

Experience in the Management of Fractures and Dislocations. By the Staff of the Fracture Service, Massachusetts General Hospital, Boston. Under the general editorship of PHILIP D. WILSON, M.D. 1036 pages; 26.5 × 18.5 cm. J. B. Lippincott Co., Philadelphia. 1938. Price, \$15.00.

The thousand page volume, "Experience in the Management of Fractures and Dislocations," by Wilson endeavors to simplify, as nearly as possible, the treatment of skeletal injuries and the practical application of the various appliances that are now in vogue. The treatise deals with the actual study of cases and analyzes the results both immediate and late. The data compiled by some 30 odd writers along with methods of treatment for each individual fracture make this work probably one of the most inclusive of any single volume yet written on the subjects of fractures and dislocations. The general practitioner, specialist, and teacher in this important branch of surgery will find this book a valuable reference.

T. B. A.

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Reprints

Dr. William G. Bernhard (Associate), Newark, N. J.—2 reprints;
Dr. Dean B. Cole, F.A.C.P., Richmond, Va.—4 reprints;
Dr. Willard J. Davies, F.A.C.P., Rockville Centre, N. Y.—2 reprints;
Dr. Harold H. Golz (Associate), Clarksburg, W. Va.—1 reprint;
Dr. J. Edwin Habbe, F.A.C.P., Milwaukee, Wis.—9 reprints;
Dr. A. A. Herold, F.A.C.P., Shreveport, La.—2 reprints;
Dr. Cullen Ward Irish, F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. Jerome G. Kaufman (Associate), Newark, N. J.—1 reprint;
Dr. Elmer A. Kleeffeld (Associate), Forest Hills, N. Y.—1 reprint;
Dr. Louis H. Landay, F.A.C.P., Pittsburgh, Pa.—1 reprint;
Dr. M. B. Marcellus, F.A.C.P., Tillamook, Ore.—1 reprint;
Dr. Leslie M. Smith (Associate), El Paso, Tex.—2 reprints;
Dr. A. C. Woofter (Associate), Parkersburg, W. Va.—2 reprints.

SECTIONAL MEETINGS OF THE COLLEGE

During the autumn months many of the College Governors will conduct sectional meetings of the Fellows and Associates in their territories. Dr. Samuel E. Munson, Governor for Southern Illinois, has announced a sectional meeting of the Illinois members at Jacksonville, Ill., on October 18, when Dr. James H. Means, F.A.C.P., Boston, will be the specially invited guest speaker.

Dr. C. H. Cocke, Governor for North Carolina, has announced a meeting of the North Carolina Fellows and Associates at Chapel Hill and Durham on October 20-21. The North Carolina program was in charge of Dr. Wilburt C. Davison, F.A.C.P., Durham, Dr. William de B. MacNider, F.A.C.P., Chapel Hill, and Dr. Verne S. Caviness, F.A.C.P., Raleigh.

A sectional meeting of the Fellows and Associates residing in the State of Virginia was held at Richmond October 4. Further reports on these meetings will be obtained and published later.

POSTGRADUATE COURSES UNDER AUSPICES OF THE COLLEGE

The Committee on Postgraduate Education and the Board of Regents will later announce the program of postgraduate courses to be offered under the auspices of the American College of Physicians during the winter and spring of 1940. Heretofore, these courses have been organized at various centers conveniently reached on the way to the Annual Session of the College and have consisted of two weeks' intensive work just preceding the Annual Session. The College made these courses available to its members at minimum cost, the College itself assuming full responsibility for promotion, advertising, printing and registration. This activity of the College will be in its third year, and due to the acclaim from those who have taken the courses

during 1938 and 1939, the program will be continued. However, the Board of Governors of the College, through its Committee on Postgraduate Survey, headed by Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, has initiated a careful study of the whole problem—the types of courses, the time when courses shall be given, means of improving the courses, etc.—with the purpose in view of making helpful recommendations to the official Committee on Postgraduate Education, headed by Dr. Hugh J. Morgan, F.A.C.P., Chairman, Vanderbilt University Hospital, Nashville, Tenn. Suggestions concerning these courses will be welcomed by the Committee. Members are urged to communicate their suggestions and recommendations directly to Dr. Morgan.

HOUSE COMMITTEE OF THE COLLEGE SOLICITS SUGGESTIONS

In the Board Room of the Headquarters of the American College of Physicians, Philadelphia, there is a wall space above a mantle, 43" broad and 36" high, which offers a splendid opportunity for an original painting or etching. The Board Room is finished in oak paneling, and the proposed painting will be the high light of the room. The House Committee desires suggestions from the membership at large, in order that an appropriate and dignified work of art may be obtained. One suggestion might represent some event in the development of medicine, preferably occurring in North America. Another possibility might be found in some historical event of importance in connection with the origin and growth of the College. The House Committee will appreciate suggestions regarding the type and subject of the proposed painting. It is also quite possible that some member might desire to underwrite the production of an appropriate subject.

Kindly address communications to the Chairman of the House Committee, Dr. Edward L. Bortz, 2021 W. Girard Ave., Philadelphia, Pa.

Dr. George H. Gehrmann, F.A.C.P., Wilmington, Del., was a guest speaker at the fifth Clinical Congress of the Connecticut State Medical Society at New Haven, September 19–21, his subject being "Industrial Poisons."

Northwestern University Medical School, through its Department of Industrial Medicine, conducted its third annual Symposium on Industrial Disease and Hygiene at Chicago on September 25–26. Dr. Herman O. Mosenthal, F.A.C.P., New York, and Dr. James P. Simonds presented a paper on "Kidney Diseases of Midlife"; Dr. Ernest E. Irons, F.A.C.P., Chicago, and Dr. Hollis E. Potter presented a paper on "Nontuberculous Pulmonary Diseases"; Dr. Walter L. Bierring, F.A.C.P., Des Moines, was the speaker at the banquet, his subject being "The Past and Future of Preventive Medicine."

Under the Presidency of Dr. John W. Scott, F.A.C.P., Lexington, the Kentucky State Medical Association held its annual meeting at Bowling Green, Ky., September 11–14. Among guest speakers and their subjects were:

Dr. Roger I. Lee, F.A.C.P., Boston, "Treatment of Artificial Menopause";
Dr. Louis Hamman, F.A.C.P., Baltimore, "Problems in Hematological Diagnosis";
Dr. Milton B. Cohen, F.A.C.P., Cleveland, "Newer Concepts of Allergy."
Dr. Frank A. Simon (Associate) and Dr. Adolph B. Loveman (Associate), both of Louisville, with Dr. Cohen and others, appeared on the Allergy Symposium program, and Dr. J. Murray Kinsman, F.A.C.P., Louisville, gave an address on "Sulfapyridine Indications, Bad Effects and Methods of Administration."

The Michigan State Medical Society held its annual meeting at Grand Rapids September 18-22, under the Presidency of Dr. Henry A. Luce, F.A.C.P., Detroit. Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., President of the American Medical Association, delivered the Andrew P. Biddle Oration (founded by Dr. Andrew Porter Biddle, F.A.C.P., Detroit). Dr. Biddle himself presented the Biddle Oration Scroll to Dr. Sleyster.

Among the guest speakers also appeared Dr. Jonathan C. Meakins, F.A.C.P., Montreal, Que., "Gastrointestinal and Hepatic Function in Congestive Circulatory Failure" and Dr. Maxwell Finland, F.A.C.P., Boston, "Treatment of Pneumonia with Sulfapyridine and Specific Serum."

Among the guest speakers appearing on the program of the ninety-eighth annual meeting of the State Medical Society of Wisconsin in Milwaukee, September 13-15, were the following:

Dr. Edward L. Tuohy, F.A.C.P., Duluth, Minn., "The Relation of Alcohol to Liver Damage" and "An Adequate Dietary in Later Life";
Dr. August A. Werner, F.A.C.P., St. Louis, "The Sex Hormones";
Dr. Alexander E. Brown, F.A.C.P., Rochester, Minn., "Sulfanilamide, Neoprontosil and Sulfapyridine and Their Clinical Applications";
Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., "The Sick Man as a Person";
Dr. Thomas J. Dry (Associate), Rochester, Minn., "Pulmonary Hypertension and Right Heart Failure."

At the last annual meeting of the New Jersey Medical Society at Atlantic City Dr. Berthold S. Pollak, F.A.C.P., Medical Director of the Hudson County Tuberculosis Hospital, Jersey City, received a citation and plaque, presented by this Society. Beneath the seal of the State Medical Society the plaque bears this inscription:

"Presented to Dr. Berthold S. Pollak for his work among the tuberculous, not only of his own county but of the State and nation, for the reflected credit accruing to our State Medical Society from his altruistic activities—1939."

The citation is one of four, the first ever to be granted specifically for work in tuberculosis by the Medical Society of New Jersey in its long history.

Dr. Albert B. McCreary (Associate), Jacksonville, Fla., has been appointed State Health Officer for Florida, succeeding the late Dr. Wilbur A. McPhaul.

At the Kentucky State Fair, Louisville, the University of Louisville School of Medicine presented a public exhibition, the specimens being taken from the pathology museum and arranged under the direction of Dr. Aura J. Miller, F.A.C.P., Professor and Head of the Department of Pathology and Serology in the Medical School.

Among the guest speakers at the seventeenth annual fall clinical conference of the Kansas City Southwest Clinical Society, October 2-5, were the following:

Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, Roentgenology;
Dr. Elliott P. Joslin, F.A.C.P., Boston, Internal Medicine;
Dr. Russell L. Haden, F.A.C.P., Cleveland, Internal Medicine;
Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., Psychiatry;
Dr. Howard B. Sprague, F.A.C.P., Boston, Internal Medicine.

Dr. Fletcher B. Taylor (Associate), Oakland, Calif., addressed the Nevada State Medical Association at its annual meeting in Reno September 22-23 on "Medical Follies of 1938."

Dr. Grant Thorburn, F.A.C.P., New York City, presided over the symposium on silicosis at the Cornell University Medical College, October 11, held under the auspices of the Tuberculosis Sanatorium Conference of Metropolitan New York.

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, has been promoted to Associate Professor of Medicine on the faculty of the University of Oklahoma School of Medicine, as recently announced by the Dean, Dr. Robert U. Patterson, F.A.C.P.

Among promotions and appointments on the faculty of the Jefferson Medical College of Philadelphia recently announced appear Dr. Garfield G. Duncan, F.A.C.P., Associate Professor of Medicine, and Dr. Creighton H. Turner (Associate), Associate Professor of Medicine.

The twenty-sixth annual meeting of the Mississippi Valley Tuberculosis Conference and the Mississippi Valley Sanatorium Association was held at Omaha, September 20-22. Dr. Hyman I. Spector, F.A.C.P., St. Louis, was President of the tuberculosis conference and Dr. William J. Bryan (Associate), Rockford, Ill., was President of the sanatorium association.

The Mississippi Valley Medical Society conducted its annual session at Burlington, Iowa, September 27-29. Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., is Secretary. Among speakers on the program appeared the following Fellows of the College:

- Dr. Charles Hugh Neilson, St. Louis, "Functional Disease" and round table discussion on "Private Practice in the Hospital";
 - Dr. Alphonse McMahon, St. Louis, "Emergency Treatment of Heart Failure";
 - Dr. Daniel L. Sexton, St. Louis, "Endocrine Therapy: Its Application in General Practice";
 - Dr. Rock Sleyster, Wauwatosa, Wis., "The Sick Man as a Person" and "Medical Problems of the Day";
 - Dr. Fred M. Smith, Iowa City, Iowa, "Treatment of Cardiac Failure" and "The Treatment of the More Common Gastro-Intestinal Disorders";
 - Dr. James H. Hutton, Chicago, banquet speaker;
 - Dr. N. S. Davis, III, Chicago, "Treatment of the Patient Who Has a Hypertensive Cardiovascular-Renal Disease";
 - Dr. Arthur L. Smith, Lincoln, Nebr., "Cardiac Arrhythmias and Murmurs."
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Dr. Shailer U. Lawton, F.A.C.P., New York City, and Dr. Edmund Jacobson, F.A.C.P., Chicago, will cover the fields of Mental Hygiene and Relaxation, respectively, in connection with a survey course in fundamentals of health education, which began at Boston University School of Education September 25 and will continue until January 22.

Dr. Merle D. Bonner (Associate), Superintendent of the Guilford County Tuberculosis Sanatorium, Jamestown, N. C., was recently honored by the Guilford County Medical Society, which presented to him a silver plaque in recognition of outstanding medical work during the year. Dr. William de B. MacNider, F.A.C.P.,

Dean of the University of North Carolina School of Medicine, was the principal speaker.

Dr. Rufus S. Reeves, F.A.C.P., was installed as President of the Philadelphia County Medical Society on September 20, succeeding Dr. Francis F. Borzell.

Dr. Conley H. Sanford, F.A.C.P., has been appointed Professor and Head of the Department of Medicine at the University of Tennessee College of Medicine, Memphis, succeeding Dr. James B. McElroy, F.A.C.P., who has resigned because of ill health. It is reported that Dr. McElroy, however, will continue as Professor. Dr. Lucius C. Sanders, F.A.C.P., has been made Assistant Professor of Medicine.

Dr. Harry Walker, F.A.C.P., has been promoted to Associate Professor of Medicine on the faculty of the Medical College of Virginia, Richmond.

Dr. Burt R. Shurly, F.A.C.P., Detroit, was the guest of honor and delivered an address before the forty-fourth annual meeting of the American Academy of Ophthalmology and Otolaryngology, Chicago, October 8-13.

Dr. W. Bernard Kinlaw, F.A.C.P., formerly of Rocky Mount, N. C., is now established in the practice of Cardiology and Internal Medicine at 195 Hempstead Ave., Rockville Centre, N. Y.

OBITUARY

DR. C. HERBERT BELKNAP

The untimely death of Dr. C. Herbert Belknap—the result of an automobile accident, May 4, 1939—was a great shock to his many friends in the profession.

A man of modest mien, kindly in nature, always with a pleasant smile and a cheery word, he was very popular with his confrères.

The esteem in which he was held, both by the medical profession and his patients, was evidenced by the large number in attendance at his funeral.

Dr. Belknap had perhaps one of the largest practices in Detroit. Born November 5, 1891, at Eden, N. Y.; B.S. degree, University of Illinois, 1911; M.D., Detroit College of Medicine (Wayne University), 1916; Intern, Grace Hospital, 1916-17; Assistant in Physiotherapy Service, 1926-29, Grace Hospital; Assistant Attending Physician, 1932-35, Grace Hospital; Associate Attending Physician, 1935 to date of death, Grace Hospital; Vice Chief, Department of Hyperthermia, Grace Hospital.

Dr. Belknap served two years in the U. S. Army—discharged with the rank of Captain (M.C.) U. S. A., August 1, 1919.

C. Herbert Belknap was elected Associate of the American College of Physicians at the New Orleans Session, April 1939. While in New Orleans he was married to Miss Buchanan, and had been home but a short time before his untimely death.

GEORGE BARRIE HOOPS, M.D., F.A.C.P.